UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA DE LISBOA

COGNITIVE FUNCTIONS DURING MIGRAINE ATTACKS

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DOUTORAMENTO em MEDICINA

ESPECIALIDADE de NEUROLOGIA

2015

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Dissertação orientada pela Professora Doutora Isabel Pavão Martins

Tese especialmente elaborada para obtenção do grau de

Doutor em Medicina, Especialidade de Neurologia

JÚRI

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2015

A impressão desta dissertação foi aprovada pelo Conselho Científico da Faculdade de Medicina da Universidade de Lisboa em reunião ocorrida a 23 de Julho de 2015.

Abstract

Background: Attack-related cognitive symptoms in migraine are frequent yet scarcely characterized and undervalued as contributors of disability. Conflicting evidence arose about an increased risk of cognitive decline in older migraine patients.

Objectives: (1) to study the occurrence of cognitive symptoms in migraine attacks; (2) to evaluate objective evidence of cognitive dysfunction in migraine attacks and its neuronal correlates and (3) to study the effect of persisting migraine in cognitive function or cognitive decline in older adults.

Methods: Occurrence of attack-related cognitive symptoms was detailed by systematic literature review and a cross-sectional clinical-based systematic survey; their relevance to disability was studied prospectively using headache diaries. An instrument (Mig-SCog) was developed, validated and tested to identify and quantify attack-related subjective cognitive symptoms. Cognitive function during attacks was evaluated by a systematic literature review and a clinical-based prospective two-period randomized cross-over study using an extensive neuropsychological battery. A briefer battery was tested in repeated applications in interictal patients and controls. Brain perfusion during attacks was studied with arterial spin labeling magnetic resonance imaging (ASL-MRI) and cortical response to a working memory task with blood-oxygen level dependent functional magnetic resonance imaging (BOLD-fMRI). A prospective controlled cross-sectional population-based study of neuropsychological performance of older adults with persisting migraine and non-migraine headache was followed by a 5 years re-evaluation of the same sample, to screen for cognitive decline.

Results: Cognitive symptoms were the most frequent non-migraine defining symptoms reported in the prodromic(37%) and headache(38%) phases of migraine attacks in a systematic review of 28 series, with a total sample of 8392 patients. Cognitive symptoms are also present in the postdromic or resolution phase, although fatigue (71%) is reported more often. Of 165 patients prospectively surveyed, 87% reported an average

of 2.5 attack-related symptoms, over two-thirds executive (attention, processing efficiency and speed). Cognitive symptoms were ranked prospectively by 34 migraine patients recording 229 attacks, being second only to pain in terms of intensity and attack-related disability. An instrument to quantify migraine attack-related symptoms was constructed from a set of 43 candidate items, using factor analysis. The reduced 9 item Mig-SCog is fast to apply covering executive functions and language, having good internal consistency (Cronbachs' alpha 0.82) and reliability (Cohen's kappa 0.55) and high correlation with external validity measures such as the 43-candidate item list (rho=0.69) and the Cognitive Failures Questionnaires(rho=0.61). The Mig-SCog presents negligible recall bias (no difference in scores obtained during an attack or while headache free) and Migraine patients score it higher for migraine higher for migraine (7.9±4.6) than for non-headache pain (2.3±2.9, $p<0.0006$) or pain free (1.6±2.4, $p<0.0006$). Comparing Mig-SCog scores in migraine and tension-type headache patients, those were higher for migraine in all scale items ($p<0.0001$) except those related to naming (8 and 9). The AUC of Mig-SCog score for the diagnosis of Migraine was 0.835 (95% CI of 0.763-0.906, $p< 0.0001$) reinforcing specificity for migraine.

Ten studies of neuropsychological evaluation during migraine attacks are available in the literature, only half had data allowing comparison of cognitive performance within and outside attacks (encompassing 163 migraine patients). All these were able to demonstrate some type of impairment (most often executive) although some bias could not be excluded from their study design. In our sample of 24 patients which completed an extensive neuropsychological evaluation in these two conditions (attack and headache-free) controlling for the majority of relevant bias (in particular the practice effect), performance was worse during the attack in the majority of cognitive tests, in particular in word reading speed ($p=0.013$), verbal learning ($p=0.01$), short term verbal recall with ($p=0.01$) and without ($p=0.013$) semantic cueing and delayed recall with ($p=0.003$) and without ($p=0.05$) semantic cues. Another sample of 24 interictal migraine patients and 24 matched controls performed equally in a shorter battery focused on executive functions that was applied twice with a short interval (average 45 days) to test the practice effect of repeated evaluations that was demonstrated in all tests, being significant in Stroop Interference test ($p=0.002$, multiplicity corrected); a meaningful score change was determined for each raw test scores.

We were unable to find any relevant brain perfusion nor brain activation differences evoked by a working memory task during a spontaneous migraine without aura attack of an average intensity of 6.8 on a 0-10 VAS scale and an average duration of 16 hours in a sample of 13 women, compared to being headache-free.

Persistent migraine or headache after the age of 50 related to worse performance in some neuropsychological tests (attention and processing speed in migraine patients, n=61; sematic memory and memory retrieval in non-migraine headache, n=50) in a population sample of 478 individuals tested extensively. After 5 years, 275 (57.5%) of the same sample were screened for cognitive decline, that occurred in 14.9% of the sample. Neither migraine nor non-migraine headache influenced the odds of decline.

Discussion: Attack-related cognitive symptoms are very frequent, mostly executive and contribute to disability, supporting that they should be addressed as endpoint in clinical trials of acute migraine treatments and included in disability assessments. An efficient way to assess attack-related subjective cognitive symptoms in clinical practice or research is now available – the Mig-SCog. Although migraine-related reversible cognitive dysfunction was demonstrated during attacks, no advances on potential brain mechanisms underlying these findings were made. Interest is focused to obtain more functional data, with studies of evoked activation paradigms, functional connectivity and combined imaging and neurophysiological studies. Although persisting headache in older adults seems to influence executive performance, these changes are most likely adaptive and do not seem to influence the process of brain degeneration and associated cognitive decline.

Key Words

Migraine, Headache, Neuropsychology, Cognition, Functional Neuroimaging.

Resumo

Introdução: Os sintomas cognitivos que ocorrem durante a fase álgica das crises de enxaqueca são muito frequentes, no entanto foram pouco estudados e sobretudo pouco valorizados como potenciais contributos para a incapacidade funcional verificada durante as crises. A relação entre sintomas referidos pelos doentes e a efetiva disfunção cognitiva nas crises é inconsistente; a mais, não existe uma explicação fisiopatológica evidente nas já conhecidas alterações do funcionamento cerebral associadas à crise de enxaqueca que sejam potencialmente relacionáveis com este tipo de disfunção. A potencial persistência de queixas cognitivas na fase intercrítica em doentes com enxaqueca é controversa mas, a existir, poderá contribuir para um potencial aumento de risco de declínio cognitivo nestes doentes.

Objetivos: Este projeto de investigação apresenta 3 objetivos principais: (1) estudar a ocorrência de sintomas cognitivos durante as crises de enxaqueca; (2) avaliar a ocorrência de disfunção cognitiva objetivável e do seu substrato neuronal e (3) estudar o efeito da persistência da enxaqueca até idades tardias (acima dos 50 anos) na função cognitiva e no risco de declínio cognitivo.

Métodos: A ocorrência de sintomas cognitivos durante a crise de enxaqueca foi estudada inicialmente através da realização de uma revisão sistemática da literatura que permitiu recolher e classificar os principais sintomas já descritos. Em seguida procedeu-se à aplicação de um inquérito sistematizado numa amostra de base clinica de doentes com enxaqueca episódica. A perceção da relevância destes sintomas para a incapacidade atribuível à crise de enxaqueca foi estudada prospectivamente com diários de enxaqueca numa outra amostra de base clínica de doentes com enxaqueca episódica. Foi desenvolvido e validado um novo instrumento (Mig-SCog) que permite identificar e quantificar de forma sistemática os sintomas cognitivos subjetivos associados às crises de enxaqueca. Este instrumento foi testado de forma a avaliar a sua especificidade para a enxaqueca e a sua reprodutibilidade.

De forma a avaliar a efetiva ocorrência de disfunção cognitiva na fase álgica das crises de enxaqueca foi efetuada uma revisão sistemática da literatura avaliando todos os estudos que efetuaram avaliação neuropsicológica em doentes durante as suas crises de enxaqueca. Atendendo às limitações encontradas, foi realizado um estudo prospetivo cruzado e randomizado efetuando uma avaliação neuropsicológica extensa de um grupo de doentes durante uma crise de enxaqueca sem aura e no seu estado normal, livre de dor. Adicionalmente foi montada e testada num estudo transversal controlado uma bateria neuropsicológica breve e prática que permitisse aplicações repetidas, em doentes com enxaqueca. Os potenciais mecanismos cerebrais subjacentes à disfunção cognitiva associada às crises foram estudados inicialmente comparando a perfusão cerebral durante uma crise espontânea de enxaqueca sem aura com a fase intercrítica aplicando um método quantitativo de avaliação de perfusão baseado em Ressonância Magnética, denominado *Arterial Spin Labeling Magnetic Resonance Imaging* (ASL-MRI). Na mesma amostra de doentes foi adicionalmente estudado o padrão de resposta cortical a uma tarefa cognitiva executiva (memória de trabalho) utilizando outro método de Ressonância Magnética, denominado *Blood-Oxygen Level Dependent functional Magnetic Resonance Imaging* (BOLD-fMRI).

Foi efetuado um estudo transversal populacional controlado avaliando o desempenho neuropsicológico em adultos com enxaqueca ou outras cefaleias que mantinham as suas crises após os 50 anos de idade sendo esta amostra posteriormente reavaliada longitudinalmente (após 5 anos) de forma a determinar o risco de declínio cognitivo nesta população.

Resultados: Os sintomas cognitivos são dos sintomas mais consistentemente descritos nas fases prodrómica (37% casos) e na fase álgica (38% casos) das crises de enxaqueca, identificados numa revisão sistemática de 28 séries clinicas envolvendo uma amostra total de 8392 doentes. Este tipo de sintomas também está presente nas restantes fases da crise, embora na fase posdrómica ou de resolução o sintoma predominante seja a fadiga (71% dos casos). Em 165 doentes questionados prospectivamente, 87% descrevem em média 2.5 sintomas cognitivos distintos ocorrendo durante as suas crises, cerca de 2/3 destes relacionáveis com sintomas executivos – sobretudo de atenção, eficiência e velocidade de processamento. As queixas de domínio cognitivo foram classificadas por 34 doentes registando prospectivamente 229 crises como o segundo

sintoma mais importante (a seguir à dor, em si mesma) responsável pela intensidade e incapacidade atribuível à crise de enxaqueca. Foi desenvolvida e validada uma escala prática e específica para identificar e quantificar os sintomas cognitivos subjetivos que ocorrem durante as crises, a partir de um conjunto de 43 itens candidatos desenvolvidos após entrevistas a doentes e revisão bibliográfica, utilizando analise fatorial. A escala obtida, de 9 itens (Mig-SCog), é de rápida aplicação e foca-se nos domínios de funções executivas e de linguagem, apresentando uma boa consistência interna (alfa de Cronbachs' 0.82), fiabilidade (kappa de Cohen 0.55) e uma elevada correlação com medidas de validade externa, tais como a lista candidata de 43-itens (rho=0.69) e o questionário de falhas cognitivas (rho=0.61). A Mig-SCog apresenta um viés de memória negligenciável (não se verificaram diferenças nos resultados obtidos durante as crises e os reportados fora de crise) e resultado final verificado para a enxaqueca é mais alto (7.9±4.6) do que para uma dor somática (2.3±2.9, $p<0.0006$) ou em relação a estar sem dor (1.6±2.4, $p<0.0006$). O resultado do Mig-SCog é superior em doentes com enxaqueca do que em doentes com cefaleia de tensão em todos os itens da escala ($p<0.0001$) exceto nos itens de nomeação (8 e 9). A AUC do resultado total do Mig-SCog para o diagnóstico de enxaqueca foi 0.835 (95% CI de 0.763-0.906, $p<0.0001$) reforçando a sua especificidade para a enxaqueca.

Uma revisão da literatura identificou 10 estudos em que foi efetuada uma avaliação neuropsicológica durante as crises de enxaqueca, no entanto apenas 5 (incluindo 163 doentes) apresentavam dados comparáveis de avaliação fora de crise. Em todos estes estudos foi possível identificar disfunção cognitiva na crise através da utilização de testes neuropsicológicos, em particular testes computorizados de funções executivas e testes convencionais (em papel) de leitura e velocidade de processamento, memória verbal e aprendizagem, muito embora não se pudessem excluir vieses importantes devido ao desenho dos mesmos. Na nossa amostra de 24 doentes que completaram uma avaliação neuropsicológica extensa em duas condições (numa crise e fora de crise) controlando a maioria dos vieses relevantes (em particular, o do efeito de aprendizagem) foi possível documentar um declínio de desempenho na maioria dos testes efetuados, em particular na velocidade de leitura ($p=0.013$), aprendizagem verbal ($p=0.01$), memória verbal de curto termo com ($p=0.01$) e sem ($p=0.013$) ajuda semântica e memória verbal de longo termo com ($p=0.003$) e sem ajuda semantica($p=0.05$).

Na fase intercrítica, 24 doentes com enxaqueca tem um desempenho idêntico a controles emparelhados numa bateria breve de avaliação neuropsicológica contendo sobretudo testes executivos. Os testes desta bateria foram avaliados em aplicações repetidas num intervalo curto (em média 45 dias) para testar o efeito de aprendizagem, que foi demonstrado em todos os testes, sendo significativo no Stroop Interferência (p=0.002, corrigido para a multiplicidade). Foi quantificada a variabilidade mínima com potencial significado clínico.

Os estudos de perfusão cerebral não conseguiram identificar alterações significativas de perfusão global ou regional durante as crises de enxaqueca sem aura, quando comparadas com a fase intercrítica numa amostra de 13 mulheres avaliando uma crise com uma intensidade média de 6.8 (numa escala visual de 0-10) e uma duração média de 16 horas. Do mesmo modo, nem o desempenho nem a ativação cerebral obtida com uma prova de memória de trabalho foram diferentes nestas duas condições, na mesma amostra de doentes com enxaqueca sem aura.

A persistência de crises de enxaqueca e de outras cefaleias após os 50 anos foi associada com um declínio de desempenho nalguns testes neuropsicológicos de atenção e velocidade de processamento (na enxaqueca, n=61) e de memória semântica e recuperação de informação mnésica (noutras cefaleias, N=50) quando comparados com controlos sem cefaleias numa amostra de base populacional de 478 indivíduos testados em todos os domínios cognitivos. A reavaliação de 275 (57.5%) indivíduos da mesma amostra após 5 anos permitiu estimar o risco de declínio cognitivo em cerca de 14.9% da amostra, no entanto este risco não foi influenciado pela presença de enxaqueca nem de outras cefaleias.

Discussão: A ocorrência de sintomas cognitivos durante as crises de enxaqueca é muito frequente. Os sintomas mais consistentemente descritos são atribuíveis às funções executivas, o que pode ser devido a uma seletividade específica das alterações do funcionamento cerebral associadas à crise de enxaqueca para o sistema executivo ou à relevância deste tipo de funções no funcionamento do dia-a-dia, em particular com o desempenho laboral e nas interações sociais. De acordo com a perceção dos doentes, estes sintomas contribuem de forma relevante para a incapacidade associada à crise de enxaqueca, substanciando a necessidade de incluir medidas subjetivas ou objetivas de

disfunção cognitiva como parâmetros de avaliação de eficácia nos ensaios clínicos de fármacos para controle da crise, assim como em medidas ou escalas de avaliação da incapacidade. A documentação objetiva destes sintomas é possível através de testes neuropsicológicos no entanto não existe ainda uma medida prática ou universal que permita a sua quantificação de forma fiável. Foi desenvolvido e validade um instrumento fiável e específico que permite quantificar a existência de sintomas cognitivos subjetivos durante as crises (o Mig-SCog), sendo facilmente aplicável em contexto clínico ou em investigação. A determinação dos mecanismos cerebrais potencialmente implicados na fisiopatologia destes sintomas é difícil e os dados disponíveis não permitem ainda a construção de um modelo teórico consistente. Os estudos de perfusão cerebral permitem distinguir os processos cerebrais ocorrendo durante as crises de aura (que condicionam hipoperfusão cortical) dos processos que ocorrem nas crises sem aura (sem hipoperfusão), sugerindo mecanismos fisiopatológicos distintos para estas duas fases da crise. O interesse futuro está focado agora na obtenção de mais dados de estudos funcionais, quer estudos com paradigmas de ativação evocada, quer de conectividade funcional ou mesmo estudos combinados de imagem e neurofisiologia. Apesar de as cefaleias e/ou enxaqueca persistentes após os 50 anos terem influência no desempenho cognitivo executivo desta população (de forma idêntica à documentada noutras situações de dor crónica ou recorrente), estas alterações são mais provavelmente adaptativas e reversíveis e não parecem influenciar o processo normal de envelhecimento ou degeneração cerebral nem do declínio cognitivo associado à idade.

Palavras Chave

Enxaqueca, Cefaleias, Neuropsicologia, Cognição, Neuroimagem funcional

ACKNOWLEDGMENTS

The author wishes to express sincere appreciation and gratitude to Professora Doutora Isabel Pavão Martins for her guidance in the preparation of this dissertation and for her continuous support and friendship that has always been present in my life, in the last 20 years. More than a teacher, she has always been an example, a personal reference and a true friend – undoubtedly, my mentor. I have no words to thank her enough, I can only wish to be worthy of her trust, to be able to keep up with her enthusiasm and live up to her expectations.

Also, my deepest gratitude to my friends and also co-authors, Professor Doutor António Gouveia de Oliveira that has guided and helped me through the world of statistics even from across the Atlantic Ocean, with huge professionalism and continuous support and Dr. Pedro Ferro Vilela, that has been a wonderful working colleague, a good supporting friend and was co-responsible for the design and data analysis of the imaging studies.

This work would not have been possible without the help of a group of people that contributed kindly and willingly with their work, each in their own areas. Special thanks to Ms. Isabel Santos, for her extraordinary work in bibliographic support; Dra. Luísa Albuquerque that helped with classification of data in one of the studies; Dra. Teresa Durães, Ms. Andreia Silva and all the administrative and assistants team of Hospital da Luz, for their friendship and help in organizing my everyday life and to find me time to work in this project and to my working colleague, Dra. Sofia Oliveira, for the extra work she had to endure while I was writing this dissertation. I also thank the MRI technicians (The "Neuro-Team") Ana Filipa Graça, Ana Cristina Santos, Cidália Martins, Fernando Gonçalves e Ruben Teixeira that were always able to accommodate research studies disturbing everyday work and did it a joyful and effective way; to the nurses of the Hospital da Luz, represented by Nurses Ana Santos Pereira and João Graça, for their inexhaustible help in selecting the candidates for the studies; to Rita Alcoforado and Rita Eça, the research secretaries, that supported each of the projects willingly with their time, expertise and resources; to the neuropsychologists Susana Rodrigues, Catarina Chester and Clara Loureiro, for their help and professionalism during the neuropsychological projects. Last, but certainly not least, to the patients and volunteers that participated enthusiastically in the research projects without any kind of personal compensation.

For their presence in my life as examples of professionalism, integrity and expedition, my sincere thanks to Professora Doutora Isabel Pavão Martins, Engenheira Isabel Vaz, Professor Doutor José Roquette, Professor Doutor José Ferro and Dra. Luísa Albuquerque.

I must end by acknowledging the spice of my life, my dear Nuno and the most gorgeous and sweet kids of the World, Alexandre, Cristina e Filipe; my loving Mum and Dad, my Grandparents and all the rest of the family that are, thank God, too many to write down but are all in safekeeping, in my heart.

FINANCIAL SUPPORT

The following projects were funded:

- Cognitive dysfunction during migraine attacks.

  This study was financed by the Portuguese Headache Society – Tecnifar investigation grant 2002.

  The design, conduction, management, analysis, interpretation of the data of this study was done by the authors without any financial compensation. Preparation, review and approval of the manuscript were also done by the authors without any financial compensation. The grant was used to support neuropsychologists work (neuropsychological evaluations) that was related to data collection and database preparation.

- Magnetic Resonance Imaging of a Migraine without aura attack – brain perfusion study using ASL-MRI and fMRI study using the N-Back paradigm.

  This study was financed by the Portuguese Headache Society – Tecnifar investigation grant 2010.

  The design, conduction, management, analysis, interpretation of the data of this study was done by the authors without any financial compensation. Preparation, review and approval of the manuscript were also done by the authors without any financial compensation. The grant was used to support the cost of the imaging studies, supporting material and neuropsychological evaluations.

- Migraine, Headaches and Cognition.

  This study was financed by the Research Grant from Fundação Calouste Gulbenkian (Project 0488) and from BIAL (63/10) as a part of a larger study, ‘‘Mindful Aging: Avoiding Age-Related Cognitive Decline’’.

  The design, conduction, management, analysis, interpretation of the data of this study was done by the authors without any financial compensation. Preparation, review and approval of the manuscript were also done by the authors without any financial compensation. The grant was used to support neuropsychological evaluations.

LIST OF PUBLICATIONS

1. Gil-Gouveia R, Martins, IP. *Clinical Description of attack-related cognitive symptoms in Migraine. A systematic review. [Submitted]*
2. Gil-Gouveia R, Oliveira AG, Martins IP. *Subjective Cognitive Symptoms during the Migraine attack. A prospective study of a clinic based sample.* Pain Physician 2016 *[in press]* Impact Factor: 4.77
3. Gil-Gouveia R, Oliveira AG, Martins IP. *The impact of cognitive symptoms on migraine attack-related disability*. Cephalalgia 2015 Sep 8 *[Epub ahead of print]* Impact Factor: 4.12;
4. Gil-Gouveia R, Oliveira AG, Martins IP. *A subjective cognitive impairment scale for migraine attacks – the MIG-SCOG: development and validation*. Cephalalgia 2011; 31(9):984-91. Impact Factor: 4.12;
5. Gil-Gouveia R, Oliveira AG, Martins IP. *Clinical Utility of the Mig-SCog*. *[Submitted]*
6. Gil-Gouveia R, Oliveira AG, Martins IP. *Assessment of cognitive disorders during migraine attacks: A systematic review*. Journal of Neurology 2015 Mar;262(3):654-65. Impact Factor: 3.84
7. Gil-Gouveia R, Oliveira AG, Martins IP. *Cognitive dysfunction during migraine attacks: A study on migraine without aura.* Cephalalgia 2015 ;35(8):662-74 Impact Factor: 4.12;
8. Gil-Gouveia R, Oliveira AG, Martins IP. *Sequential evaluation of migraine patients and controls using a short battery of cognitive assessment*. Acta Neurol Scand 2015 *[in press]*
9. Gil-Gouveia R, Pinto JS, Figueiredo P, Vilela PF, Martins IP. *An Arterial Spin Labeling MRI perfusion study of Migraine without aura attacks*. *[submitted]*
10. Gil-Gouveia R, Pinto JS, Figueiredo P, Vilela PF, Martins IP. *Executive function in migraine without aura attacks. An fMRI study using the N-Back paradigm. [in preparation]*
11. Martins IP, Gil-Gouveia R, Silva C, Maruta C, Oliveira AG. *Migraine, headaches and cognition.* Headache 2012 Nov-Dec; 52(10):1471-82 Impact Factor: 3.19;
12. Gil-Gouveia R, Loureiro C, Martins IP. *Migraine, headaches and cognition – a follow-up study on cognitive decline. [in preparation]*

STATEMENT OF CONTRIBUTIONS OF OTHERS

The following co-authors contributed to the projects and publications contained in this Thesis:

Professora Doutora Isabel Pavão-Martins contributed fully in all projects included in this thesis, in particular in study conception and design, analysis and interpretation of data and critical revision of all the manuscripts. In the studies about *Migraine, headaches and cognition* contributions also included data acquisition and manuscript drafting. Prof. Isabel Pavão-Martins made a critical revision of this Thesis.

Professor Doutor António Gouveia Oliveira contributed significantly in most of the projects included in this thesis, except the *Clinical Description of attack-related cognitive symptoms in Migraine. A systematic review, An Arterial Spin Labeling MRI perfusion study of Migraine without aura attacks* and *Executive function in migraine without aura attacks. An fMRI study using the N-Back paradigm.* He contributed in study design, statistical analysis and interpretation of data and in critical revision of the manuscripts.

Doutor Pedro Ferro Vilela contributed significantly in the two MRI projects included in this thesis, *An Arterial Spin Labeling MRI perfusion study of Migraine without aura attacks* and *Executive function in migraine without aura attacks. An fMRI study using the N-Back paradigm.* His contributions included study conception and design, acquisition analysis and interpretation of data and in critical revision of the manuscripts.

Joana Sequeira Pinto and Professora Patrícia Figueiredo contributed in the two MRI projects included in this thesis, *An Arterial Spin Labeling MRI perfusion study of Migraine without aura attacks* and *Executive function in migraine without aura attacks. An fMRI study using the N-Back paradigm.* Their contributions included study design, acquisition analysis and interpretation of data and in critical revision of the manuscripts.

Claudia Silva, Carolina Maruta and Clara Loureiro contributed in the studies about *Migraine, headaches and cognition.* Their contributions included help in study design, acquisition, analysis and interpretation of data and in critical revision of the manuscripts.

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1. Introduction

INTRODUCTION

Historical Perspective

The oldest record containing the description of an headache syndrome dates from around 4000 BC, identified in Babylonian cuneiform tablets (1), although it is believed that trepanation was performed for relieving evil spirits causing headache, madness and seizures from inside the head, much earlier, in the Neolithic period (9000 BC)(2). More detailed clinical records were found in several Egyptian papyri, including the Ebers papyrus (1550 BC). Ebers papyrus includes a syndromic description of migraine(3) and even describes an episode in which Ra, the solar deity which was believed to have created all forms of life and to rule all parts of the world (the sky, the earth and the underworld)(4), was given an headache after using some lesser deities remedies intended to cure of all his ills. It was Isis, the goddess of motherhood, magic and fertility, that used a mixture of honey and plants including the "berry-of-the-poppy-plant" (an opium poppy) that drove out the pain in Ra's head(5).

The first description of a visual aura followed by a migraine headache was made by Hippocrates of Kos (400 BC)(6) and the first detailed description distinguishing migraine from other headaches and including in the migraine syndrome all symptoms that are currently mandatory criteria for migraine diagnosis(7) was made by the Greek Aretaeus of Cappadocia (30–90 A.D.)(8). In this text he already included details about attack related humor changes "…*torpor, heaviness of the head, anxiety, and ennui*…", as well as co-morbid reactive depression "…*are weary of life, and wish to die*". The Roman Galen of Pergamon (121-200) further described several headache entities, introducing the terms *hemicrania*, *cephalalgia* and *cephalaea* to distinguish between headache types. He also published observations that implicated the stomach, the meninges, the pericranium and cranial blood vessels in migraine etiology(8). The *treatise de Medicina* wrote by another Roman, Aulus Cornelius Celsus (25–50 A.D.), includes the first clear description of attack-related cognitive symptoms in migraine: "*In the head, then, there is at times an acute and dangerous disease, which the Greeks call cephalaia; the signs of which are hot shivering, paralysis of sinews, blurred vision, alienation of the mind, vomiting, so that the voice is suppressed, or bleeding from the nose, so that the body becomes cold,*

vitality fails. In addition there is intolerable pain, especially in the region of the temples and back of the head." (9).

Byzantine physicians (330-1453) maintained the theory of Galen, on which the humors of the body and head explained migraine, relating the stomach and the head in the concept of "bilious headache" that also ensued in the medieval Persian medical books(8). In the 12th century, the Benedictine abbess, philosopher and physiologist Hildegard of Bingen considered her own visual auras as spiritual visions, influencing a mythic interpretation of migraine by the Catholics in the following century(10). In the 13th and 14th centuries, most of the medical treaties about headache focused on herbal-based treatments(10). It was not until the 17th and 18th centuries that innovative discussion on headache pathogenesis and treatment erupted.

European physicians such as the Dutch Nicolaas Tulp (1593–1674 A.D.) described various types of headaches including Cluster headache(8) and the English Thomas Willis (1621–1675 A.D.) was the first to provide the description of premonitory symptoms of migraine, that included fatigue, bursts of energy and hunger (10). The first medical book focusing on headache was published by Edward Liveing(11) (1832–1919 A.D.), in which he included various detailed clinical description of the syndrome, including observations on hereditability, epidemiology, natural history, and about the attack in itself – triggers, prodromes, visual, sensitive and aphasic auras (interpreted as epileptic phenomena), pain and accompanying symptoms. Cognitive symptoms were described as a disturbance of "ideational consciousness"; a clear reference to disturbance of higher cerebral faculties is described under the sub-title of "Psychical Phenomena", in chapter III, "Phenomena of the Paroxysm"(11). He divided these phenomena in "intellectual" and "emotional", describing the former as "...impairment of memory and in confusion and incoordination of ideas..", ".. confusion of thought..", "…unable to collect his thoughts…", "…feeling silly…", "…loosing their senses…", although it is often not clear if some of these descriptions are related to the aura or the headache phase of the attack. The "emotional" phenomena were clearly stated to start in premonition of the attack, complaints of "…irritability of temper…", "ill-humor" and a "vague and unaccountable sense of fear…" could precede the attack by one or two days, and "great mental depression" could linger through the entire paroxysm(11). In his

treaty he also included chapters on migraine pathology, co-morbidities and treatment. By the end of the 19th Century the dominant view was that migraine resulted from a cerebral disturbance, an "excess of nervous system energy", as defended by Willian Gowers (1845-1915) in is *Manual of Diseases of the Nervous System(8)*.

During the 20th century, migraine research derived from clinical aspects to exploring migraine pathogenesis, genetics and treatment; some of the relevant scientific advances in migraine research were about these areas – migraine pathogenesis was initially related to vascular changes, due to the identification of intracranial vascular changes (1938) and of pain structures in the head (1940) and then the theory was shifted to a neuronal etiology, after the analysis of spreading scotoma of visual aura (1941), its relation to cortical spreading depression of Leão (1944), the documentation of the spreading oligemia of migraine with aura (1981) and the identification of the first gene for familial hemiplegic migraine (1996). Further evidence integrating these phenomena was added by the theory of neurogenic inflammation (1984), the identification of the "brainstem generator" (1995) and of the central sensitization mechanism and allodynia (1996)(12). Therapeutic weaponry was initiated with the clinical introduction of ergotamine (1918), the identification of serotonin (1959) and later with the advent of the triptans (1988). The discovery of Calcitonin Gene-Related Peptide (CGRP) (1990) probably heralds a range of therapeutic targets for next generation drugs(12). The clinical major breakthrough of the 20th Century was the establishment of a consensus basis for diagnosis of headache disorders, the international headache classification (1988, 2004, 2013)(7, 13, 14), that allowed better definition and higher quality research and therapeutic trials. With the widespread use of the classification the focus was set on diagnosis and diagnostic criteria and the study of other clinical aspects of migraine became less expressive. In particular, cognitive symptoms almost ceased to be mentioned in clinical series of migraine and only a handful of studies approach the existence and meaning of these attack-related symptoms.

The Migraine Attack

Migraine is the third most frequent disease in the world, affecting 14.7% of the World population(15), but after puberty the female gender has thrice the prevalence of males. While the prevalence in prepubescent individuals is low, it increases particularly in the most productive working years, between the third and fourth decades of life (24% of women and 7% of man), then declines to around 6.5% in women and 5% in man after the sixth decade (16). Migraine characteristics also seem to change with age, attacks being less typical in young and older patients(17), and headache frequency seems to decline with age(18).

Migraine is a chronic disorder with episodic manifestations of syndromic attacks, occurring on average 2.1 per month that can last from 4 to 72h, their average length being around 32h40 minutes(19, 20). The attacks can be divided in four phases: prodromes, aura, pain and resolution or postdromes(21). During an attack, most patients are not able to function normally – 33% report severe disability (completely impaired for any activity) 47% moderate disability (partial impairment), 18% mild disability and only 1% report being functional(16). Burden of Migraine is calculated estimating in 5.3% the proportion of time spent in the symptomatic (ictal) state and in 43.3% the disability assigned to migraine episodes, resulting in migraine being ranked as the seventh highest among specific causes of disability globally (responsible for 2.9% of all Years Lived with Disability, YLDs)(15).

The premonitory phase of the migraine attack includes symptoms attributed to migraine that start as far as 3 days before the actual headache or pain onset, but most often within the 24h preceding the painful phase(22); average prodrome duration is around 9 to 10 hours(21, 23). Interpreting these symptoms or premonitory signs, patients are able to predict the occurrence of the attack, with an increasing accuracy that ranges from 20% in the previous day to 90% 2 hours before pain onset(22). Not all patients experience prodromes, prevalence estimates range from 7 to 88% (22-24) yet prodromes can be distinguished from unspecific symptoms occurring in the interictal

phase(25) and some prodromes are noticed by patients family members or social interlocutors(26). Prodromes usually persist up to the point of pain onset(27) yet often do not resolve at this point nor with the end of the headache, persisting through the resolution phase, or the posdrome(22).

The prodromes were initially distinguished from the other more exuberant phenomena preceding the onset of pain - the aura – for having insidious onset, lasting several hours and affecting mood, behaviour, wakefulness, gut motility and fluid balance suggesting potential hypothalamic dysfunction in this phase, supporting the view of migraine as a neurogenic disorder(21). It was not until recently, with functional neuroimaging, that hypothalamic involvement in the early stages of the migraine attack was documented (28, 29), supporting the potential role of this structure in the prodromal phase of the attack, although in one study it's activation persisted thru the pain and pain relief(29). The role of the hypothalamus in migraine can be either as a generator or trigger sensor for the attack (supported by the association of attack triggering to sleep disturbances and hormonal fluctuations)(30, 31) or in nociceptive modulation(32). Its dysfunction can explain both autonomic symptoms(33) and mood changes, through its connections to the limbic system(34).

The aura is a rare and complex neurological event occurring in around 15% of migraine patients. Most patients(81%) do not experience auras in every migraine attack(35). The most frequent clinical manifestation of aura is visual, being present in 65 to 99% of patients with aura. Other symptoms that may be present are sensory (31%), aphasic (18%) and motor(6%), occurring in various combinations (36, 37), although the designation of "typical" aura includes visual, sensory and aphasic symptoms in succession, as defined in the International Classification of Headache Disorders (ICHD-III) (7).

The clinical hallmark of a migraine aura is the progression of symptoms over time (lasting around 15 to 30 minutes(35)), with progressive symptom resolution of one type or one location preceding the onset of the next symptom or site; also the simultaneous presence of positive and negative symptoms(7, 36). Not all auras are followed by a headache - as much as 10% have isolated auras(36). most patients (55%) have less than 1 attack per month and it's most frequent duration is 15 to 30 minutes(35), although 12

to 37% of patients can have episodes lasting longer than 1 hour(38). The presence and type of aura and/or headache determines the subdivision of migraine diagnosis in the ICDH-III(7).

Karl Spencer Lashley in 1941, describing his own visual auras, was able to map and rate the progression of visual symptoms across the visual field to a rate of propagated at a rate of 3 mm/minute or less, describing the typical excitatory expanding scintillating fortification figures followed by the inhibition scotoma and progressive recovery(12) now consistent with typical visual aura. This typical and consistent progression of symptoms had a neurophysiological correlate, the phenomenon of Cortical Spreading Depression (CSD), described by Aristides Leão in 1944, as a cortical wave of spreading electrical excitation followed by depression occurred and propagated at a rate of 3 mm per minute occurring in rabbits' brains after mechanical or chemical stimulation(39). It was not until the advent of functional neuroimaging studies that it was possible to observe an similar phenomena translated into BOLD (Blood-Oxygen Level Dependent) signal changes in the living human brain cortex during a migraine aura (40).

The pain of migraine starts within the aura phase in as often as 54% of attacks(41), while the remaining have an average free interval between the end of the visual aura and headache onset that is usually shorter than 30 minutes (35). During this free interval, some patients fell completely well while others describe mood changes, perception difficulties, cognitive changes and somatic symptoms(42) being unclear is these symptoms represent the lingering or onset of prodromes after the aura(22, 23, 25, 27). The headache is the most frequently occurring phenomena of migraine and its characteristics define the diagnosis of Migraine(7). The head pain is typically unilateral (bilateral in 25 to 40%) throbbing (47 to 91%) or pressing (90%) moderate to severe, mostly felt in the trigeminal sensory distribution (eyes 67%, temporal 58%, frontal 56%) or neck (40%). Headache onset is usually progressive with a median time to peak of around 90 minutes and pain is aggravated by activity in 53 to 90% of patients. Headache lasts in average 6 to 24 hours and its average intensity of the attack in episodic migraine is around 8/10 on a Visual Analogue Scale(20, 43, 44) although the classification only requires pain to be moderate to severe and to last from 4 to 72hours(7).

Migraine pain is associated with several non-painful symptoms such as photophobia (increased sensitivity to light, in 55 to 97% of attacks), phonophobia (increased sensitivity to normal-volume auditory stimuli in 47 to 95%), osmophobia (hypersensitivity to odors in 25 to 75%) and kinesiophobia (intolerance to movement in 53 to 98%) and nausea (80 to 87%) and vomiting (44 to 67%) (20, 44-47) but not all need to be present to allow diagnosis(7).

Pain is thought to be a consequence of the activation of the trigeminovascular system by the cortical release of neurochemical mediators by the Cortical Spreading Depression (CSD). The activated perivascular nociceptive trigeminal sensory afferents release CGRP and nitric oxide with consequent sterile neurogenic inflammation (vasodilatation, plasma protein extravasation and mast cell degranulation) that further activates meningeal nociceptive trigeminal sensory afferents, explaining the pain projection on the trigeminal territory. This information travels to the trigeminal ganglion, then the brainstem trigeminocervical complex and up to the thalamus, were it is integrated as a nociceptive input in the pain matrix of the brain(48). Dysfunction of structures involved in the modulation of neuronal excitability and pain, such as the periaqueductal grey and the locus coeruleus in the brainstem, the thalamus and even reduced activation of descending cortico-trigeminal inhibitory pain pathways are thought to be responsible for symptoms accompanying the headache, such as allodynia, photophobia, and phonophobia(49).

The headache will at some point decrease progressively, either imperceptibly or quickly until it disappears, even without any specific intervention to shorten the attack(50). Attacks can then be shortened or interrupted by several strategies, the most common being medication, sleep or vomiting(50). However, 60 to 94% of patients have up to seven(25, 50-52) different persisting migraine symptoms after headache resolution, that last on average 25.2 hours (< 12h in 54% of patients; although most patients (39 to 60%) have postdromal symptoms consistently, only 26% have them in all attacks(25, 52). The more complete or typical is the migraine attack, the higher the probability of having posdromal symptoms(52).

Little is known about the mechanisms that underlie the attack resolution nor the posdrome; given the fact that many of the posdromal symptoms are also present in the

prodromal phase of the attack, it was proposed that this phase would represent a slow decline or resolution of the brain process activated since the beginning of the attack that had been overshadowed by headache, and could theoretically involve the same brain structures, such as the hypothalamus(51). This is supported by functional imaging studies that reveal persistence of dorsolateral pons, midbrain and hypothalamic activations after headache relief with sumatriptan(29, 53); nevertheless, the effects of medication used to treat the attack may also have an impact of symptoms arising after the painful phase has subsided (52, 54, 55).

Clinical and physiological data(56) supports that the migraine attack starts before pain onset and does not end with pain relief; although patients can distinguish attack phases, the transition between phases is arbitrary, or even variable. Even considering the time lapse in between migraine attacks - the interictal phase - there is evidence of differences of brain function in migraineurs, compared to controls. As an example, migraine patients are more likely to be light-sensitive and their cortical responses to light are triggered with a lower threshold than matched controls even in the absence of pain(57). This increased responsiveness of the migraine brain to an external stimuli seems to be mediated by cortical information processing abnormalities that translate into reduced amplitude of early responses and lack of the normal decrease in mean amplitude of responses with repeated visual, auditory, somatosensory or cognitive stimuli (habituation) in the interictal phase, reverting to normal function just before and during an attack(58).

Description of cognitive difficulties occurs in all phases of the attack and some reports suggest their occurrence also in the interictal phase (59, 60).

Cognitive Functions

Cognitive Function can be generally defined as the conscious and unconscious mental process by which one becomes aware of concepts or ideas; it involves a wide range of brain functions, such as perception, reasoning, memory, language, learning etc.; these functions have complex interactions that influence emotions and behaviors(61).

The study of cortical cytoarchitecture by Broadmann (1909) generated the concept that the cerebral cortex differences in the organization were related to specific cortical functions; the cortex was then divided into sensory, motor, association (areas processing information from a sensory modality) and multimodal association cortex (areas integrating information from different modalities), reflecting the functional specialization of specific brain areas. Later, neurophysiological studies have identified patterns of neuronal responses organized in functional columns in the brains' neocortex; these cortical columns have multiple cortical-cortical and cortico-subcortical reciprocal connections and are organized into functional subsets or nodes, each belonging to a number of connected functional systems(62). Brain systems are collections of processing units that are spatially separate yet connected and communicating, being the basis of the brains' functional integration ability. The organized action of these systems supports complex brain operations, such as the higher brain functions(62).

To study higher brain functions cognitive neuropsychologists assume that there is a meaningful relationship between the organization of the brain and that of the mind and also that cognitive processes can be viewed as modules, being relatively independent from each other - a classical view coming from the study of brain lesions(63). The principal methods used to study mental capacities rely on direct observation, behavioral checklists, semi-structured interviews and formal neuropsychological tests or psychometric tools, in which an experimental standardized measurement of performance in a specific function or task is applied and compared with normalized populations of interest(64).

Functional imaging has revolutionized the study of brain functions and its' mapping in the last 20 years as it has allowed the identification of brain areas of higher

energy consumption (measured by local changes in blood flow, metabolism and tissue oxygenation) associated with the performance of specific tasks, changes assumed to be the reflexion of increased neuronal activity(65). Studying evoked brain activity lead to astonishing advances in identifying functional specialization of cortical and subcortical areas but studying temporally related patterns of activations and deactivations allowed the identification of large-scale intrinsic brain activity patterns that were denominated as "resting state" networks, believed to be the basis for mind-wandering and related forms of spontaneous thought (66).

Although the study of cognitive functions has greatly expanded it is still very complex not only due the limitations of each technique but especially to the determination of meaningful changes and to the definition of "normality". Cognitive performance is able to be influenced by many variables, examples including sleep deprivation(67), hypo or hyperglycaemia(68, 69), heat or cold exposure(70, 71), positive or negative mood changes(72, 73), effects of nicotine(74), caffeine(75) or alcohol(76) also of many drugs including stimulants or sedatives(77, 78), effects of literacy(79) or musical training(80) and particularly age, as cognitive performance progressively improves from childhood to adulthood and slowly declines with further aging (81, 82).

Cognitive functions decline in normal aging is not homogeneous; perceptual speed and numerical ability start to decline from early adulthood (mid-twenties) while verbal ability, inductive reasoning, verbal memory, episodic memory and verbal fluency decline starts from the fifties on (83, 84); the impact of the aging process is not uniform amongst healthy individuals conditioning important variability. In addition, several health problems accelerate age-related cognitive decline and are risk factors for dementia, such as lack of environmental stimulation physical inactivity, obesity, smoking, vascular comorbidities (diabetes, hypertension, hyperlipidemia), neuropsychiatric symptoms, and low dietary folate intake (85-87).

Pain is also able to influence cognitive functioning; acute pain has been shown to modify the cerebral activity pattern induced by a cognitive task(88); in chronic pain a correlation between the level of cognitive dysfunction and pain ratings has been documented, as was an improvement in cognitive performance with effective pain control(89). Although the mechanism underlying the pain-cognition interaction is not defined, it is well known that the several of cortical areas through which pain is generated from nociception (the ‘‘pain matrix’’)(90) can be activated in several cognitive settings. In theory, recurrent nociceptive inputs may compete with cognitive information processing; also neuroplastic and neurochemical changes resulting from chronic pain induce brain processes reorganization that may interfere with cognitive processes(89, 91).

2. Objectives and Research Outline

THE RESEARCH PROBLEM

Migraine is the third most prevalent disease in the World, being the seventh highest specific cause of disability globally (responsible for 2.9% of all Years Lived with Disability, YLDs)(15). This Global Burden of Migraine assessment is exclusively based on attack related disability yet the identification and valorization of the specific attack symptoms producing migraine-related disability is not consensual(92-94).

Headache is the hallmark of migraine and its most consistent disability-related symptom, yet headache relief does not always translate into functional recovery(54); in particular, difficulties in performing cognitive tasks are pointed out as important contributors to attack-related disability(54, 93, 95).

Attack-related cognitive symptoms in Migraine are described in medical texts at least since the first century(9) yet detailed knowledge about these symptoms occurrence, characterization or physiopathology is scarce in medical literature. Objective documentation of reversible cognitive dysfunction during migraine attacks seems to be consistent, although most of the studies supporting this findings are small and bear some methodological limitations (60, 96-100). No systematic way to identify or quantify these symptoms exists, that would allow better characterization of its frequency or impact.

Migraine is currently perceived as a complex brain disorder in which several cortical and subcortical structures interplay in a given sequence or pattern, giving rise to different clinical expressions of the same phenomenon in an orchestrated plot. The frequency of repetition of these events is associated to structural brain changes, documented in synaptic density (grey matter) and connectivity (white matter)(101). Imbalance of cortical or subcortical influences may underlie cognitive symptoms perceived by patients during attacks(60, 96-100, 102, 103).

Although migraine is clinically more relevant and expressive at young-adult age, persisting attacks at late adult life or in the elderly could potentially influence the normal pattern of cognitive age-associated decline, as pain itself is known to influence cognition(89). Evidence from large population-based longitudinal studies does not seem to support an increased risk for cognitive decline in migraine patients although some studies are able to identify interictal differences in some cognitive functions of migraine patients, compared to healthy controls (104, 105).

Improving the knowledge about cognitive function during migraine attacks can provide clues to the brain processes occurring within the attack and help determining the sequence of brain events producing the episodic brain dysfunction of migraine patients. It can also help to understand potential mechanisms contributing to cognitive changes or adaptations to these repetitive dysfunctional events occurring with normal aging in migraine patients.

Potential applications include (1) Development of better disability measures for migraine, that include cognitive dysfunction; (2) Inclusion of cognitive outcomes in trials of acute attack medication (with potential impact in reducing migraine-attack related disability); (3) Developing new therapeutic targets related to the brain mechanisms involved in migraine attack-related cognitive dysfunction.

OBJECTIVES

Objective #1:

To study the occurrence of cognitive symptoms in migraine attacks

- Identify, collect and systematize information about subjective cognitive symptoms occurrence during migraine attacks, based on data available on published peer-reviewed medical literature

- Describe and classify, in a clinical series of migraine patients, the subjective cognitive symptoms most often reported during the headache phase of migraine attacks

- Determine the intensity and disability of attack-related cognitive symptoms in a clinical series of migraine patients and to relate it with intensity and symptom related disability of migraine attack defining symptoms.

- Develop a quantitative and practical instrument to identify and quantify attack-related subjective cognitive symptoms in migraine (Mig-SCog)

- Document the specificity of the Mig-SCog for migraine

Objective #2:

To evaluate objective evidence of cognitive dysfunction in migraine attacks

- Identify, collect and systematize information about objective cognitive dysfunction documented by neuropsychological testing during migraine attacks, based on data available on published peer-reviewed medical literature

- Compare cognitive performance of migraine without aura patients during and outside attacks using an extensive battery of neuropsychological tests and controlling for the most important potential confounders in this context

- Assemble a brief neuropsychological battery to identify and quantify objective executive dysfunction in migraine

- Document brain perfusion changes occurring during migraine without aura attacks using the Arterial Spin Labeling Magnetic Resonance Imaging (ASL-MRI) technique.

- Document brain responses to a cognitive (executive) challenge during and outside a migraine without aura attack using Blood Oxygen Level Dependent functional Magnetic Resonance Imaging (BOLD-fMRI)

Objective #3:

To study the effect of persisting migraine in cognitive function or cognitive decline in older adults

- Compare objective cognitive function evaluated with extensive neuropsychological testing in healthy older adults without headache, with migraine and non-migraine headache

- Determine the effect of migraine and headache on cognitive decline of healthy older adults

RESEARCH OUTLINE

Research question #1 - *Are cognitive symptoms included in clinical series of migraine patients describing the migraine attack phenomenology?*

A systematic review of medical databases (Medline and Cochrane Library) was performed to identify and collect available data about cognitive symptoms occurrence in any phase of the migraine attack. Due to the high variability of the retrieved studies' methodologies, data analysis was qualitative; symptoms were grouped into domains and each phase of the attack was evaluated independently. Tables with symptom frequency were plotted for each phase of the attack (prodromes, aura, pain and posdromes).

Research question #2 – *What attack-related cognitive symptoms do migraine patients report? Is there a pattern?*

A cross-sectional systematic survey about the occurrence of cognitive symptoms during the headache phase of migraine attacks was performed in a clinical-based sample of 165 episodic migraine patients in two phases; data from the initial 93 patients of this sample was also used to in the study of the development of the Mig-SCog. In this study, however, the sample was increased to improve the quality and consistency of symptom reporting. Data collection started with a dichotomic (yes/no) question regarding the occurrence of such symptoms followed by an open-ended question regarding spontaneous description of each symptom. Finally, a self-administered symptom checklist was used to confirm the preceding spontaneous symptom elicitations, which included subjective cognitive (executive, spatial perception and language) and non-cognitive (mood, anxiety and visual) symptoms.

Symptoms prompt as answers to the open-ended question and of the symptom checklist were classified and grouped into cognitive and non-cognitive domains, and within each domain into different functions and plotted into frequency tables. The relation between having cognitive symptoms during attacks with demographic and disease-related variables was sought.

Research question #3 - *Are attack-related cognitive symptoms relevant to migraine-attack related disability?*

The migraine attacks of an independent clinical-based sample of 100 episodic migraine patients were prospectively recorded using paper headache diaries. Information collected included items of timing of the recorded attack (pain onset and relief, timing of rescue medication use) and scoring on a 0-10 Visual Analogue Scale the intensity and disability related to each attack and to each migraine symptom, including also two cognition related symptoms - pain worsening with mental effort and difficulty in thinking. Relationships between intensity and disability scores of the attacks an of each migraine symptom were explored.

Research question #4 – *Can we identify and quantify attack-related cognitive symptoms in migraine?*

An extensive (43 items) cognitive symptoms checklist was assembled based on structured interviews of 37 migraine patients and with data from literature review in order to develop a questionnaire that allows identification and quantification of subjective cognitive symptoms in migraine attacks. The extensive checklist was applied prospectively to an independent sample of 93 migraine patients and factor analysis was conducted for item reduction. The reduced checklist retained 9 items that composed a multiple choice self-administered questionnaire – the Mig-SCog. Construct validity, internal consistency, temporal stability and external validity of the questionnaire were tested.

Research question #5 – *Are cognitive complaints identified with the Mig-SCog specific for migraine? How reliable is the Mig-SCog?*

The Mig-SCog was prospectively applied in a clinical-based sample of headache patients in three different prospective studies with independent patient samples –one cross-sectional comparing migraine (N=98) and tension-type headache patients (N=51); the remaining included migraine patients using Mig-SCog for three different status (migraine, non-headache pain and pain-free, N=63) and in the last study the Mig-SCog was fulfilled within and in-between attacks, to screen for the recall bias (N=38). Scores obtained in each situation were calculated and compared with the appropriate statistic method. Validity analysis was used to determine the sensitivity and specificity of the Mig-SCog for the migraine diagnosis.

Research question #6 – *What is the evidence of cognitive dysfunction occurrence during migraine attacks?*

A systematic review of medical databases (Medline and Cochrane Library) was performed to identify and collect available data about the existence and pattern of impaired neuropsychological performance during migraine attacks, compared to the headache-free status. Due to the high variability of the retrieved studies' methodologies, data analysis was qualitative; Tables with summaries of relevant results were plotted.

Research question #7 - *Do migraine patients have reversible cognitive impairment during attacks?*

A prospective two-period randomized cross-over study of neuropsychological performance of clinic-based independent sample of 39 migraine patients within a spontaneously occurring migraine without aura attack and in the headache-free period was conducted. Patients' performance in an extensive neuropsychological battery was compared between both situations, while controlling for the most relevant potential bias.

Research question #8 – *How can we measure attack-related cognitive impairment?*

A battery composed of brief and practical routine neuropsychological tests focused on executive functions was assembled in order to be possible to sequentially test migraine patients in their ictal or/and inter-ictal status. A prospective cross-sectional controlled study of the performance of inter-ictal migraine patients in repeated short-term (6 weeks) applications of this battery was conducted. Cases' performance was compared to that of matched controls, using a convenience sample of 48 volunteers from the hospital staff. The practice or learning effect of each test was quantified in order to determine the clinically meaningful predictable score change of repeated applications.

Research question #9 - *Do brain perfusion changes exist during migraine without aura attacks?*

A prospective longitudinal study of brain perfusion using Arterial Spin Labeling magnetic resonance imaging (ASL-MRI) was conducted in 13 female episodic migraine patients recruited among the hospital staff and in the acute care outpatient clinic during an untreated spontaneously occurring migraine without aura attack and repeated in a headache-free period. Cerebral global and regional brain perfusion was averaged for the total group and subtracted between the two sessions in order to identify perfusion differences.

Research question #10 – *Are there neuronal network abnormalities underlying the attack-related executive symptoms in migraine?*

The previous study was complemented by the evaluation of cortical activation using Blood Oxygen Level Dependent functional magnetic resonance imaging (BOLD-fMRI) in response to an executive task (N-Back) and a brief neuropsychological evaluation focused on executive functions in the same conditions, during an untreated spontaneously occurring migraine without aura attack and repeated in a headache-free period. The cortical activation pattern in response to the N-Back task was averaged for the total group and subtracted between the two sessions in order to identify activation differences. The performance on the neuropsychological evaluation was compared between the sessions and differences found were paralleled to the predictable score change of repeated applications.

Research question #11 - *Is ongoing migraine related to worse cognitive performance late in life?*

A prospective cross-sectional population based study of older adults (aged 50 or over) neuropsychological performance in an extensive neuropsychological battery was undertaken. The headache status of the sample was sought and classified into migraine, non-migraine headache and headache-free individuals, whom were used as controls. Cognitive performance was compared between groups.

Research question #12 - *Is migraine associated with an increased risk of cognitive decline later in life, compared to other headaches or being headache-free?*

The same sample of the previous study was revaluated after five years, to screen for cognitive decline, defined as a significant decline in memory and/or executive functions. The influence of persisting headache (migraine or non-migraine headache) on the risk of cognitive decline was sought.

3. Subjective Cognitive Complaints during Migraine Attacks

SUBJECTIVE COGNITIVE COMPLAINTS DURING MIGRAINE ATTACKS

CHAPTER FOREWORD

The following chapter is devoted to the study of the subjective perception of cognitive difficulties by migraine patients during migraine attacks – their cognitive symptoms. Description of cognitive difficulties is frequent in the clinical setting and patients' perceptions relate these symptoms to working and social interaction disability during attacks.

The existence of attack-related cognitive symptoms in migraine seems to be consistent throw-out historical medical descriptions at least since the first century(9). A systematic review of the most recent medical literature seeking the identification and characterization of this symptomatology is first presented, supporting that these symptoms are frequently described in clinical series of migraine patients and are included in all phases of the migraine attack (prodromes, aura, headache and posdromes). The most frequent symptoms report to executive functions (concentration difficulties, impaired thinking and slow processing) and language.

As the headache phase is the most relevant in clinical terms, a prospective survey ensued which had the aim to improve knowledge about the symptoms most often described in this phase of the attack. The majority of patients felt cognitive symptoms during the headache phase of the migraine attack and their descriptions were fairly consistent and characterized by complaints of attention difficulties, diminished cognitive efficiency and processing speed impairment. An exhaustive description of patients' symptoms using their phraseology is provided to help the clinicians to acknowledge patients' cognitive difficulties.

The following step was trying to document, by using patients' perceptions, if these symptoms had relevant impact on the migraine attack. Over two-hundred migraine attacks were evaluated prospectively with diaries scoring each migraine symptom intensity and disability on a 0-10 Visual Analogue Scale. Cognitive symptoms were scored second only to pain in terms of intensity and attack related disability, raising awareness about the need to treat this relevant and overlooked part of the attack.

To improve awareness about these symptoms there is a need to go beyond their identification. Cognitive symptoms' complex nature and heterogeneity hampers the perception of their impact, therefore the need for a standardized instrument with the ability to identify and quantify cognitive symptoms during migraine attacks. The Mig-SCog was developed and validated to this purpose.

The Mig-SCog is a 9-item self-fulfilled, easy to apply and very brief questionnaire reflecting subjective impairment in two cognitive domains (executive functions and language) that was developed for migraine. Its clinical applicability was further tested and it has shown to be consistent, highly specific for migraine (compared to tension-type headache) patients and had a negligible recall bias. This instrument can be of help both in clinical practice and in clinical trials to monitor treatment effects on attack-related cognitive symptoms.

Clinical description of attack-related cognitive symptoms in Migraine. A systematic review.

Gil-Gouveia R, Martins, IP.

Clinical Description of attack-related cognitive symptoms in Migraine. A systematic review. [Submitted]

ABSTRACT

Introduction: Documentation dating back to the Roman Era in the first Century comprises cognitive symptoms in the clinical description of the migraine attack. This important part of the migraine syndrome has been neglected through the centuries despite being a potentially valuable contributor to migraine-related disability.

Objective: To determine if cognitive symptoms are included in clinical series of migraine patients describing the migraine attack phenomenology and if specific cognitive symptoms are present in each phase of the migraine attack.

Method: Systematic reviewed of existing data on clinical description of the migraine attack, focusing on accompanying cognitive symptomatology. Data was organized and analyzed qualitatively, due to methodological differences between studies.

Results: Twenty-eight articles were reviewed, with a total sample of 8392 migraine patients, 37.1% with aura, 82.7% females with an age average of 39.6 years. Twenty one (75%) studies focused only on one phase of the attack (8 prodromes, 5 aura, 1 between aura and pain, 3 headache and 4 postdromes), the remaining studied more than one attack phase. Cognitive symptoms were the most frequent group of symptoms reported in the prodromic(37%) and headache(38%) phases, while fatigue(71%) dominated the postdromic or resolution phase. Not enough data is available to estimate the frequency of cognitive symptoms during the aura.

Discussion: Cognitive symptoms are consistently described in all phases of the migraine attack phenomenology in published clinical series of migraine patients and its occurrence seems to be different in different phases of the attack. Important methodological limitations prevent accurate interpretation of this findings.

INTRODUCTION

Migraine is the third most frequent disease in the world, affecting 14.7% of the World population(15), and its prevalence is particularly high in the most productive working years(16).

Migraine is a chronic disorder with episodic manifestations of syndromic attacks; during an attack, most patients are not able to function normally – 33% report severe disability (completely impaired for any activity) and 47% moderate disability (partial impairment) (16). Burden of Migraine is calculated estimating in 5.3% the proportion of time spent in the symptomatic (ictal) state and in 43.3% the disability assigned to migraine episodes, resulting in migraine being ranked as the seventh highest among specific causes of disability globally (responsible for 2.9% of all Years Lived with Disability, YLDs)(15).

Migraine attacks are complex phenomena that start before the onset of pain. The elaboration of the International Headache Classification(14) has boosted the study of migraine by providing a simple definition focusing on the most expressive symptoms of the syndrome; the downside was that many more ill-defined, less expressive symptoms have been overlooked in the most recent years of migraine research. Some of these symptoms might be as common or as disturbing as pain itself or may provide important clues to the pathology of the brain process underlying the migraine attack and to the identification of relevant therapeutic targets for minimizing attack-related disability. One of such examples is attack related allodynia(106, 107); another might be migraine attack-related cognitive dysfunction(108, 109), which has a potential clinically relevant impact on attack disability.

This study objective is to perform a systematic literature review to provide detailed information about non-migraine defining symptoms occurring during the migraine attack, focusing on cognitive symptomatology. The specific search questions were: Are cognitive symptoms included in clinical series of migraine patients describing the migraine attack phenomenology? If so, in which phase of the migraine attack (prodromes, aura, pain and posdromes) are they noticed by patients? Are different

symptoms described in different phases of the attack? Can a frequency of their occurrence be estimated, based of published data?

METHODS

Search Strategy

Potentially eligible studies were identified through electronic databases search of Medline (through PubMed) and the Cochrane Library from inception to November 2014, without any limitations or restrictions. The search used the free text terms “migraine” AND “prodromes” OR “premonitory”, “migraine” AND “aura”, “migraine” AND “pain” “migraine” AND “prostdrome” OR “resolution”, and combined with “cognition” OR “cognitive” OR “neuropsychological” and with “cognitive” OR “executive” OR “memory” OR “language”- We additionally searched “migraine” AND “cognition” and “migraine” AND “clinical characterization”. The thesaurus terms used in these searches were "Headache" OR "Headache Disorders" OR "Migraine Disorders" OR "Migraine with Aura" AND "Cognition" OR "Cognition Disorders” AND “clinical medicine”.

Study Selection and Data Collection

Titles and abstract screening identified studies that described any type of cognitive symptom occurring in any phase of the migraine attack, including reviews, clinical series and research studies. Studies were excluded in title or abstract screening if they reported (1) cognitive testing or test results in migraine patients (2) cognitive symptoms associated with treatments used in migraine patients; (3) cognitive symptoms of chronic migraine and/or medication overuse headache or genetic forms of migraine (CADASIL, Familial Hemiplegic Migraine); (4) clinical characterization of migraine patients that did not include cognitive symptoms; (5) psychological or psychiatric symptoms in migraine patients; (6) cognitive or cognitive behavioral therapy in migraine patients; (7) letters or comments; (8) small series (less than 10 patients) or case reports; (9) papers in which clinic characterization of attacks referred exclusively to ICHD defining symptoms. References of relevant papers and references of reviews were also screened with the same criteria and selected papers were retrieved and evaluated thought the same process.

Data extraction and analysis

Tables were constructed to summarize the included studies and relevant results from the studies selected. The data was organized, classified and analyzed qualitatively; different symptoms were grouped according to its characteristics into mood/ behavioral, migraine-related (including sensorial and gastrointestinal symptoms), cognitive or neuropsychological and autonomic symptoms. Each phase of the attack (prodromes, aura, headache and postdromes)(21, 50) was evaluated independently. Study designs, objectives and outcome measurements were very discrepant, nevertheless a few basic quantitative analysis were made to allow data organization, including (1) Averaging the frequency of each symptom between studies (considered only if there were at least 3 different studies with frequency values for any given symptom);(2) Total number of different symptoms reported within each group. Ethics committee authorization was not required as this study reviewed previously published data.

RESULTS

1. **Study flow and Details**

The study flow is depicted in Fig. 1. A total of 28 papers met the eligibility criteria for review and their characteristics are depicted in Table 1; four of these papers are abstracts from a poster presentations (110-113). The majority(82%) of the studies had prospective data collection, data collection was mostly done by questionnaires (12 studies), only one study was controlled(114) - table 1.

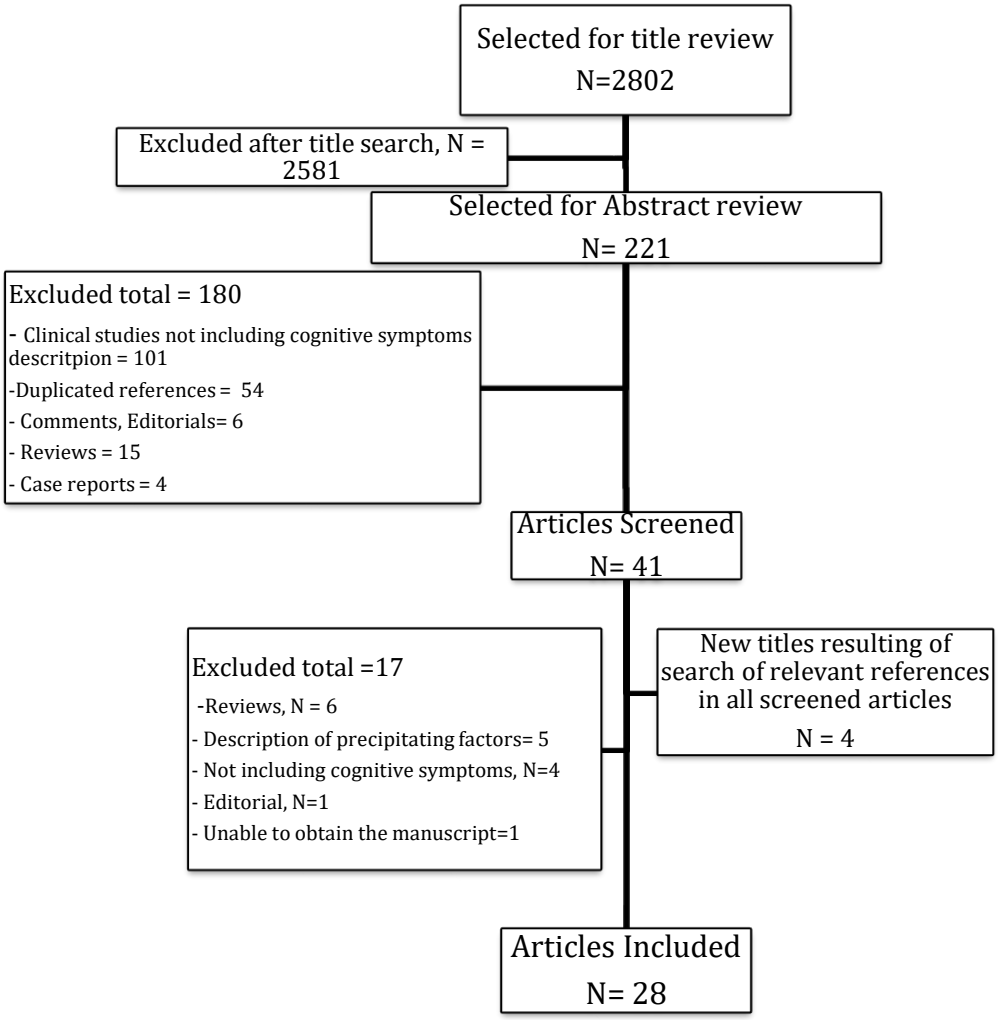
Table 1 – Summary of included studies

Study	Migraine Phase				Method					Population			
	Prodromes	Aura	Pain	Postdromes	Prospective	Retrospective	Data collection	Clinic sample	Population	Sample Size	MwA : MA	♀:♂	Age Average
Lance 1966(20)		+	+		+		Structured Clinical interview	+		500	176: 324	375: 125	NI
Blau 1980(21)	+				+		Clinical interview	+		50	31: 19	28: 22	34
Blau 1982(50)				+	+		Clinical interview	+	+ †	50	34: 16	35: 15	42

Waelkens 1985 (27)	+	+	+		+		Clinical interview	+		49	30: 19	38: 11	38
Amery 1986 (26)	+		+		+		Self-fulfilled Questionnaire		+	149	58: 91	124: 25	42
Bana 1986(37)		+				+	Clinical interview	+		325	0: 325	248: 77	37
Ardila 1988 (115)		+			NI	NI	Clinical interview	+		20	0:20	14:6	35
Blau 1991(51)				+	+		Self-fulfilled Questionnaire	+		40	29: 11	31:9	39
Blau 1992(42)	+*	+*	+*		+		Clinical interview		+†	25	0:25	17:8	42
Queiroz 1997(35)		+			+		Self-fulfilled Questionnaire	+		100	0: 100	90: 10	40
Schoonman 2003 (113)	+				+		Questionnaire	+		364	NI	290: 74	48
Giffin 2003 (22)	+		+	+	+		Electronic diary	+		82	61: 21	78:4	42
Kelman 2004 (23)	+				+		Clinical interview+ Questionnaire	+		893	NI	760: 133	38
Quintela 2006 (25)	+			+	+		Clinical interview + Questionnaire	+		100	85: 15	82: 18	39
Kelman 2006(52)				+	+		Structured Clinical interview	+		827	473: 354	705: 122	38
Schoonman 2006 (24)	+				+		Self-fulfilled Questionnaire	+		374	179: 195	300: 74	NI
Kelman 2006(17)			+			+	Database review	+		1009	871: 138	646: 363	38
Vincent 2007 (116)		+			+		Email Questionnaire	+		143	107: 36	118: 25	37
Cuvellier 2009 (117)	+				+		Telephone interview	+		103	69: 33	46: 57	©
Gil-Gouveia 2011(118)			+		+		Self-fulfilled Questionnaire	+		93	86:7	75: 18	39
Schurks 2011(119)			+		+		Questionnaire	+∫	+∫	1675	674: 1001	1675 :0	NI
Ng-Mak 2011(54)			+	+	+		Concept Elicitation Focus Group	+		34	NI	20: 14	41
Petrusic 2013(120)		+			+		Questionnaire	+		60	0:60	44: 16	39
Houtveen 2013(121)	+				+		Electronic diary	+	+	87	54: 32	74: 13	44
Stanic 2013(112)				+	+		Clinical interview	+		500	440: 60	400: 100	NI
Radojicic 2014 (110)	+					+	Questionnaire	+		321	238: 83	282: 29	38
Sretenovic 2014 (111)	+				+		Self-fulfilled Questionnaire	+		200	145: 55	169: 31	41
Jurgens 2014(114)	+	+	+			+‡	Questionnaire	+		219	149: 70	189: 30	40

Legend: (*) This study focused on the time lapse between the end of the aura and pain onset; (†) Convenience sample of medical practitioners; (‡) Controlled study ; (∫) Sub-study of a clinical trial that recruited female health professionals © - Children

Figure 1 – Study Flow



Sample sizes varied from as little as 20 (115) and up to 1675 patients(119) , total number of patients included was 8392, 6943 (82.7%) were females, with an age average of 39.6 years. One study included only children(117), one only female patients(119), 5 studies (530 patients) only migraine with aura patients(35, 37, 42, 115, 120); in total, more than one third (3110, 37.1%) the patients studied had aura. Twenty-three (82%) studies recruited patients exclusively in headache clinics yet only 13(46%) contained information about headache impact (attack frequency, duration, disease duration or impact scales)(17, 23-27, 52, 111, 117-121) and 3 about current prophylactic and/or acute medication for headache(21, 27, 111).

Twenty one (75%) studies focused exclusively on one attack phase (8 the prodromes, 5 the aura(35, 37, 115, 116, 120), one the time lapse between the end of the aura and the beginning of pain, 3 the headache and 4 the posdromes – table 1) Further analysis will be presented within each phase of the attack.

2. Clinical Description of the Migraine Attack

2.1 Premonitory phase or prodrome

The premonitory phase includes symptoms attributed to migraine that start before the actual headache or pain onset, definitions of prodrome duration vary from as far as 3 days, but most often within the 24h preceding the painful phase(22-26). Self-reported impairment of cognitive functioning and positive start at 25-36 hours before and peak in the 12 hours preceding the attack(121); average prodrome duration was 9 to 10 hours in some studies(21, 23). Interpreting these premonitory symptoms, patients are able to predict the attack with an accuracy that ranges from 20% 24h before the attack to 90% 2 hours before pain onset(22). Not all patients experience prodromes, prevalence estimates range from 7 to 88%(22-24). Around two-thirds of children have premonitory symptoms, on average 2 different symptoms(117) while adults described an average of 12 different symptoms(26). Prodromes can be distinguished from unspecific symptoms that also occur in the interictal phase(25) and patients' family members or social interlocutors also notice changes before the attack, mostly pallor, dark rings around eyes, irritability and inactivity or excessive dynamism(26).

Most premonitory symptoms persist without increasing their intensity up to the point of pain onset(27) and often do not resolve, persisting all the way up to the posdrome(22). Patients with prodromes are more likely to have more attack trigger factors, longer duration of aura, longer time between aura and headache, longer time to peak of headache, longer attack duration(26), longer time for triptan effect, higher probability of having posdromes and longer posdrome duration(23, 26). Also they more often have attacks of aura without headache and nausea and accompanying cranial autonomic symptoms (CAS) during headaches (23). The frequency of prodrome occurrence does not seem to be influenced by age (even in children) (17, 26, 117), gender (although in one study females reported more prodromes(26)), headache

intensity or impact but seems to be lower in patients taking migraine preventives(25). The presence of aura was found to increase the risk of reporting premonitory symptoms in one study (25) but not in others(24, 26).

Cognitive symptoms are frequent as early as the prodromic phase of the attack, and are among the best predictors for the attack – difficulties with speech and reading predicted 92% and 90% of the attacks, respectively(22). One controlled study concluded that concentration difficulties, unhappiness, anxiety and yawning were the most common and consistent prodromal symptoms and were not present in the interictal period.(25).

Table 2 - Frequency of non-migraine defining symptoms in the prodromic phase of Migraine Attacks, as described in the literature

		AVERAGE	Blau 1980 **(21)**	Waelkens 1985**(27)**	Amery 1986 **(26)**	Schoonman 2003**(113)**	Giffin 2003 **(22)**	Kelman 2004 **(23)**	Quintela 2006 **(25)**	Schoonman 2006 **(24)**	Cuvellier 2009 **(117)**	Radojicic 2014 **(110)**	Sretenovic 2014 **(111)**
Mood / behavior	Fatigue / Asthenia	41	12		10-49			25.6	38	46.5	41.7	60.7	62.5
	Tiredness	32	12	6		46	72.5	25.6	31				
	Adynamic / Inactive	-			>50								
	Emotional/mood changes	39	24				24.3	23.4				61.4	62
	Irritability	30	8	10	>50		38.5		42	28.1	24.3	55.7	
	Stress/ Anxiety	19	4						46	15.2	12.6		
	Claustrophobia	-		4									
	Depression	16	4		10-49				39	17.6	1.9		
	Hyperactivity / Excited/ Euphoric	8	10				5.2		9-13	15	2.9		
Migraine-Related	Nausea	23		8.2			23.5		24	28.6	5.8		48.5
	Anorexia	-							20				
	Vomiting	-							6				
	Constipation	10	2				5.6		21				
	Diarrhea	-	2						4				
	Flatulence/ Abd. distension	-		8.2	10-49				22				
	Abdominal Pain/ GI disturbance	13		6.1				22	11				
	Phonophobia	28		6.1	>50	36	38.4	1.1	44	36.4	10.7		54.5
	Photophobia	27		8.2	>50		48.8	1.3	37		7.8		57

	Sensitive skin / hyperesthesia	4		4.1	>50		5.7		1.6				
	Smell distortion/ osmophobia	16						0.7			3.9		45
	Taste distortion	-	2					0.4					
	Paresthesia	-		6.1				0.9					
	Stiff neck	31		14.3	10-49	33	49.7	3		35	2.9	55	58.5
	Muscle ache	-		2	10-49			0.2					
	Body weakness / Clumsy	-		8.2	10-49			0.5					
	Blurred vision	24		36.7	10-49		28	3.3	26				
	Dizziness	15		20.4	10-49		22.9	1.1					
	Ear Symptoms/ Tinnitus	-		2				0.5					
	Strained / swollen head	-		25	10-49			5.6					
Cognitive	Concentration problems	37			>50		51.1		36	28.1	4.8	54.1	50.5
	Difficulty with thoughts	-					34.6						
	Difficult to read/write	-			>50		20.2						
	Difficulty speech	-					9		17				
	Hazy mind/ Intellectual disturbance	-	4		>50			1.3					
Autonomic	Pale face/ face changes	21		2	>50		17.6				43.7		
	Dark rings around eyes	-			10-49								
	Yawning	17	14	12.2	10-49		27.8	0.5	40	35.8	10.7		34.5
	Somnolence	13	2	2					35				
	Insomnia	-							27				
	Sleep disturbances	-								13.9	1.9		
	Thirst / Water craving	24					26		17				30
	Hungry	12	6	12.2	10-49		18.2						
	Food Craving	14	8				18.2	0.4	15	17.4	3.9		35.5
	Frequent urination	10	2				16.2		12				
	Fluid retention	-	2						12				
	Feeling cold/Shivering	2		4.1	>50			1.1	1.9				
	Sweating	-		2	10-49								
	Dry Mouth/ Nose symptoms	-		2				0.9					
	Sighing/ Diff breathing	-		2				0.2					

Legend : Values represent percentages reported in each series; †Average percentage was calculated for each symptom if the symptom was reported in at least 3 different studies

Thirteen (46%) of the included studies analyzed the prodromic phase of the attack, eleven studies included frequency data on non-migraine defining symptoms(table 2). Fifty different symptoms were described in the 11 studies which detailed the prodromal phase, mostly migraine-related (40%) or autonomic(30%), on average 4.1 different symptoms were reported in each study (6.8 migraine-related and 4.5 autonomic). Of all the symptoms reported consistently, the most frequently were fatigue/ asthenia(41%), mood changes(39%) and concentration problems(37%). Evaluating grouped symptom frequency, cognitive symptoms(37%) were most frequent than mood/ behavioral (26%) and others.

2.2 The Aura

The frequency of aura occurrence is around 15%, declining with age(17). Typical migraine aura age onset is around 10 to 20 years, most patients(55%) have less than 1 attack per month and it's duration is 15 to 30 minutes(35), although 12 to 37% of patients can have auras lasting longer than 1 hour(38). On a clinic based population, only 19% of patients with aura had auras in every migraine attack(35), most of the patients have the majority of their attacks without aura. Not all auras are followed by an headache, 42% of patients have some auras without headache and 10% never have headaches(36).

The most frequent clinical manifestation of aura is visual, being present in 65 to 99% of patients with aura; sensory (31%), aphasic (18%) and motor(6%) symptoms occur in various combinations (36, 37). Most visual auras are unilateral(69%) and start in the central vision field(62%); visual phenomena are variable yet photopsias, flickering lines and the zig-zag lines are present in 40 to 87% of auras(35, 36); typical fortification spectra is less frequent(20%)(35). Other visuo-perceptive changes are described during auras, such as macro/micropsia, cromatopia, acromatopsia, palianopsia, pelopsia, teleopsia, simultanagnosia or visual halucinations in 1 to 13% of aura patients(35, 115, 116, 120); some of these symptoms were also described by controls in one study(114). Less frequent symptoms are prosopoagnosia, visual agnosia(116, 120) out-of-body experiences or parasomatic ("duplicated") body phenomena(122). In a controlled study, only corona phenomenon and visual splitting were specific for migraine with aura, although many other visuo-perceptive symptoms seem to occur more frequently in aura patients(114).

Sensory symptoms are mostly unilateral (84%) and start in the hand(96%) moving up to the arm(78%), face (67%) and tongue(62%), less often to the lower limb(24%) and present as tingling or paresthesias, sometimes followed by numbness(36). Higher cortical sensory symptoms, such as hemiasomatognosia, are rare (0.5% of aura patients)(115). Aphasic symptoms may occur in up to 50% of auras (116, 120) and are most often expressive (paraphasias 76%, non-fluent aphasia 72%) although impaired comprehension (38%)(36) and/or alexia may ensue. Memory is rarely involved – anterograde or retrograde amnesia may occur in up to 18%, other phenomena being even rarer (ex. "dejá vu" and "jamais vu" phenomena, despersonalization) and some also occurred in healthy controls(116).

Calculus may also be disturbed in up to 13%(120) or auras, as well as other "mental or personality" changes, with a frequency of around 3 to 7%(37, 115, 116). Other hallucinations (gustatory, 0.5%, olfactory up to 1%(115, 123) or auditory 0.17%(124)) are described in auras.

Motor symptoms are rare, occur almost exclusively after the other clinical manifestation of the aura, are almost strictly unilateral and their progression is similar to the sensory progression– hand and arm (89%), tongue and face (44%) and foot and leg (56%), often lasting more than one hour (36, 125).

Eight(29%) studies analyzed the aura, including 39 different symptoms(table 3), mostly migraine-related (49%) or cognitive(28%), on average 2.6 different symptoms were reported in each study (4.0 migraine-related and 3.8 cognitive). Five studies had symptom frequency data available, two of which contained details about sensorial migraine related symptoms, autonomic or mood changes(27, 116). The remaining focused on neuropsychological symptoms (other than ICDH-III aura defining symptoms), only three being consistently described–language difficulties(32.8% patients), visuo-perceptive changes(28.3%) and memory(19%).

Table 3 – Frequency of non-migraine defining symptoms occurring during the aura and headache phases of Migraine Attacks, as described in the literature

		AURA						HEADACHE							
		Waelkens 1985(27)	Ardila 1988(115)	Queiroz 1997(35)	Vincent 2007(116)	Petrusic 2013(120)	**Blau 1992 (42) ***	Lance 1966(20)	Waelkens 1985(27)	Amery 1986 (26)	Kelman 2006(17)	Giffin 2003(22)	Gil-Gouveia 2011(118)	Ng-Mak 2011(54)	Schurks 2011(119)
Mood/behavior	Fatigue / Asthenia	6.1			2.8						26.8	84.3	14.0	2.9	
	Eviction/ isolation												10.7		
	Adynamia/ lethargy						16.0		4.1	> 50			26.9		
	Dysphoric/ emotional						8.0			> 50		29.9			63.0
	Irritability/ fear	10.2			4.2		24.0		8.2	> 50		41.0	50.5		
	Depression						4.0		4.1	10 - 49					
	Hyperactivity / Euphory						12.0		4.1			2.7			
Migraine-Related	Nausea	8.1					8.0	95.0	93.9	> 50	54.5			67.6	89.1
	Eructation	6.1							41						
	Abd. Distension	2.0							12.2	> 50					
	Abdominal Pain	6.1							2.0						
	Diarrhea							19			9.5				
	Constipation											6.6			
	Phonophobia	6.1							93.9	> 50	68.8			64.7	86.1
	Photophobia	8.2							100	> 50	71.1			52.9	93.0
	Sensitive skin/ hyperesthesia	2.0							40.8	10 - 49		9.3			
	Smell distortion/ osmophobia	4.1							53.1		13.6			8.8	
	Taste distortion										10.8				
	Paresthesia	6.1							22.4	10 - 49					39.7
	Stiff neck	14.3							26.5			62.8		14.7	
	Muscle ache	2.0								10 - 49	12.3				
	Body weakness	8.2							6.1					2.9	
	Clumsy						16								

	Cranial Autonomic										18				
	Feeling ill						12								
	Blurred vision	36.7		27.0					4.1	> 50		34.7		17.6	50.9
	Tinnitus	2.0							2.0						
	Dizziness	20.4							8.2	> 50	36.3	31.1		23.5	61.0
	Light head	8.2					12								
	Swelling head	24					4.0								
	Tight head/ pressure	6.1								> 50				8.8	
	Throbbing blood vessels	12.2								10 - 49					
Cognitive	Feels distant/ distracted/ slow				7.7		28.0			> 50		72.6	21.5		
	Disorientation / confusion					8.3	12.0	6.8							
	Impaired thinking						16.0			> 50		50.5	90.3	14.7	
	Color naming					13									
	Dif. speech/Language		40		4.9	53.3	20.0		10.2			39.2	25.8		24.7
	Dyscalculia					13									
	Visuo-perceptive		27.5	45.0	34.1	6.7									
	Cognitive-dysmnesic		17.5		7.7	31.7							12.9		
	Hallucinations		7.5	1.0											
	Sensorial perception		2.5				4.0								
	Automatisms		5.0												
	Apraxia					11			4.1						
	Difficulty problem fixation/ planning								6.1				31.2		
Autonomic	Pale face	2.0								> 50		32.2			
	Dark rings around eyes								2.0						
	Yawning	12.2			1.4							25.4			
	Thirst / Water craving											32.2			
	Hungry/ Food Craving	12.2			2.1							18.1			28.3
	Fluid retention														56
	Frequent urination							29.0				24.3			
	Lipothymia	2.0						12	2.0						
	Feels cold/Shivers	4.1							2.0						
	Sweating	2.0													
	Dry Mouth	2.0													

Legend : Values represent percentages reported in each series; migraine-defining symptoms are plotted in grey; (*) This study focused on the time lapse between the end of the aura and pain onset

2.3 The Headache

The painful phase of migraine starts within the aura in as often as 54% of the attacks(41); other have an average free interval between the end of the aura and headache often shorter than 30 minutes(35), although it can last 10 to 60 minutes(42). In the free interval some patients are well yet others have mood changes(60%), perception difficulties (40%), cognitive (36%) and somatic symptoms (72%)(42). It is unclear if these symptoms represent the onset of prodromes after the aura or its' persistence through the total length of the attack(22, 23, 25, 27).

The headache is the most frequent occurring phenomena of migraine, being an unilateral (bilateral in 25-40%) throbbing (47-91%) moderate to severe pain, mostly felt in the trigeminal sensory distribution (56- 67%) with progressive onset and median time to peak around 90 min., being aggravated by activity in 53 to 90% of patients. Headache lasts an average 6 to 24 hours, with an average VAS intensity of 8/10(20, 43, 44).

Migraine pain is accompanied by photophobia (55-97%), phonophobia (47-95%), osmophobia (25-75%), kinesiophobia (53-98%), nausea (80-87%), vomiting (44-67%)(20, 44-47) and cutaneous allodynia(63%)(126, 127). Cognitive symptoms can persisting from the premonitory phase(22) or start during headache(17, 20, 27, 54, 118, 119). Patients describe not being able to think or concentrate(up to 71%) nor to carry out activities such as shopping (up to 83%), work or taking care of children (60%). These symptoms are more frequent when attacks are severe and contribute to migraine associated disability(95).

One of the included studies analyzed the time between the aura and the pain and 9 (32%) the headache phase of the attack, detailing 41 different symptoms (table 3), mostly migraine-related (44%) or autonomic(22%), on average 2.7 different symptoms were reported in each study (4.6 migraine-related and 2.4 mood/ behavior). The most frequently occurring consistent symptoms were impaired thinking (51.8% patients), blurred vision (36%) and stiff neck (34.7%). Evaluating symptom frequency within each group, the most frequent were cognitive(38%), followed by mood/ behavioral (32%) and migraine related (32%). Also during pain, family or friends notice facial changes and mood swings in patients(26).

2.4 Postdromes or Resolution Symptoms

The migraine headache will at some point decrease progressively, either imperceptibly or in a faster way until it disappears, even without any specific intervention to shorten the attack(50). Attacks can also be shortened or interrupted by medication, sleep or vomiting(50). However, 60 to 94% of patients have several (on average 7 (25, 50-52)) persisting symptoms after headache resolution, that last on average 25.2 hours (<12h in 54%). The definition of the postdromal period varies in different studies, some authors even allowing the existence of mild headache in this phase(51, 52, 54, 112). The frequency of postdromes occurrence does not seem to be influenced by age(17) but it relates to having greater number of family members with migraine, having prodromes and/or aura and having higher functional impact of the attacks and having lower attack frequency(52). Some postdromes occur more frequently in certain clinical situations, for instance photophobia, phonophobia and GI upset are more frequent after migraine with aura, while somnolence and concentration difficulties occur more often in patients on preventive treatments. Most patients (39-60%) have postdromes consistently, although only 26% have them in all attacks(25, 52).

Table 4 – Frequency of non-migraine defining symptoms in the postdromic phase of Migraine Attacks, as described in the literature

		Average†	Blau 1982**(50)**	Blau 1991**(51)**	Giffin 2003**(22)**	Quintela 2006**(25)**	Kelman 2006**(52)**	Ng-Mak 2011**(54)**	Stanic 2013**(112)**
Mood/behavior	Fatigue/ Tiredness	71	52.0	67.5	88.2	55.0	71.8	88.2	72.0
	Emotional/ mood changes	-			23.5		6.8		
	Stress/ Anxiety	-				15.0			
	Irritability	22		12.5	28.5	20.0		26.5	
	Depression/ lower mood	32	56.0	42.5		26.0			4.0
	Happy/ Euphoric	15	16.0	15.0		10.0		29.4	2.0
	Introverted/ isolation	-		7.5				14.7	
	Hyperactivity	-			2.4	9.0			
Migrain	Nausea/ anorexia	18			14.8	10.0		38.2	7.0
	Constipation/ Diarrhea	12		22.5	6.8	13.0	8.4		
	Abdominal pain	-				6.0			

	Photophobia	16		12.5	36.0	26.0	2.1	5.9	
	Phonophobia	15		0.5	31.8	27.0	0.4	14.7	
	Osmophobia	-		2.5				2.9	
	Taste distortion	-		7.5					
	Sensitive skin/ hypersensitivity	-			5.2	10.0			
	Paresthesia	-					1.8		
	Cranial Autonomic	-		2.5			0.5		
	Stiff / aching neck	26		35.0	41.9		3.2	23.5	
	Reduced physical energy	34		72.5			5.2	23.5	
	Muscular Weakness	21	54.0	5.0			6.2	35.3	6.0
	Clumsy/ hungover	25		15.0			11.7	17.6	55.0
	Blurred vision	13		17.5	17.4	16.0	2.0	11.8	
	Dizziness	20			19.3		5.7	35.3	
	Head tenderness	-		57.5					
	Mild head pain	36		35.0			33.1	44.1	33.0
Cognitive	Concentration problems	35		65.0	55.5	28.0	11.7	38.2	12.0
	Diff. thoughts	-			33.4			8.8	
	Lower Intellect/ "fog"	-	56.0					14.7	
	Reduced attention span	-		55.0					
	Diff. reading/Writing	-			16.8				
	Difficulty speech	19		42.5	8.5	6.0			
Autonomic	Yawning	20	8.0	32.5	13.9	24.0			
	Thirst/ drinking more	18	8.0	35.0	32.2	15.0	0.5		
	Frequent/ lower urination	17	14.0	22.5	21.2	10.0			
	Fluid retention	-				5.0			
	Feeling cold	-				17.0			
	Less apetite	21	32.0					23.5	7.0
	Food Craving	8	16.0		15.1	9.0	0.2		0.2
	Pale face	-			21.4		0.2		
	Somnolence	-				29.0			
	Insomnia	-		0.5		12.0			

Legend : Values represent percentages reported in each series; †Average percentage was calculated for each symptom if the symptom was reported in at least 3 different studies

Seven(25%) of the included studies analyzed the posdromes, including 42 different symptoms (table 4), the most frequent being migraine-related(43%) or

autonomic(24%), on average 4.5 different symptoms were reported in each study (8.0 migraine-related and 4.0 autonomic). Of the symptoms reported consistently, the most frequent were fatigue/tiredness(71%), concentration problems(35%) and reduced physical energy(34%). Evaluating symptom frequency within each group, 35% had mood/ behavioral, 27% cognitive, 22% migraine-related and 17% autonomic symptoms. The most common postdromal symptoms reported in a study that used focus groups to detail this phase of the migraine attack were tiredness, nausea, head pain, difficulty concentrating and physical weakness(54); these patients reported that postdromal symptoms were clinically relevant, as they felt decreased physical activity, difficulty at work, difficulty performing general cognitive tasks and true impact on family and social life(54). Tiredness, asthenia and somnolence were consistent postdromes and were not felt in the interictal phase in one controlled study(25).

DISCUSSION

This review retrieved clinical information about non-migraine defining symptomatology occurring during the attack from clinical series of migraine, with a special focus on cognitive symptoms. Answering our first research question, we found 28 studies including 8392 patients, in which cognitive symptoms were described spontaneously in clinical interviews or actively sought using questionnaires, electronic diaries and even in a concept elicitation focus group. These observations support that cognitive symptoms are a part of the subjective experience of the migraine attack, consistently with early historical descriptions of migraine and with everyday clinical experience.

The oldest description of migraine (mentioning all ICHD-III(7)symptoms) made by the Greek Aretaeus of Cappadocia (30–90 A.D.)(8) already included details about attack-related mood changes "…*torpor, heaviness of the head, anxiety, and ennui*…"; the *treatise de Medicina* wrote by the Roman Aulus Cornelius Celsus (25–50 A.D.) includes the first allusion to attack-related cognitive symptoms- "*In the head, then, there is at times an acute and dangerous disease (…) the signs of which are hot shivering, paralysis of sinews, blurred vision, alienation of the mind, vomiting….*"(9). Fifteen hundred years later, the English Thomas Willis (1621–1675 A.D.) described premonitory symptoms such as fatigue, bursts of energy and hunger(10) and Edward Liveing(11) (1832–1919 A.D.)

published the first medical book about headache, were cognitive symptoms are included as disturbance of "*ideational consciousness*" found under "*Phenomena of the Paroxysm*"(11). He divided these in "*intellectual*" and "*emotional*", describing the former as "*...impairment of memory and in confusion and incoordination of ideas...*", "*… confusion of thought...*", "*…unable to collect his thoughts…*", "*…feeling silly…*", "*…loosing their senses…*"; the "*emotional*" phenomena included "*…irritability of temper…*", "*ill-humor*" and a "*vague and unaccountable sense of fear…*" and could precede the attack by one or two days, while a "*great mental depression*" would linger through the entire paroxysm(11).

Even by then, the migraine attack was described in different phases; in this review, cognitive symptoms are documented in all phases of the attack, although the pattern described in each phase could differ. The prodromes are the best studied– 46% of the studies (2991 patients) contained information about 50 different prodromal symptoms. Most were migraine-related or autonomic, supporting the view that the hypothalamus may play a role in the development of migraine attacks(28). In our pooled data, the most frequent prodromal symptoms were cognitive (due to the high frequency of "concentration problems"), and mood/ behavioral ("fatigue, asthenia and mood changes").

Studies about the aura were scarcer, only 5 (1416 patients) that described 39 different symptoms, mostly migraine-related or cognitive. These observations may be biased as it is difficult to disentangle some complex neuropsychological phenomena from more vague cognitive symptoms – an example being "speech difficulties", that may reflect true aphasia or mild everyday word finding hesitations. Also, we know that pain does not always start after the aura(41) so some symptoms relate to pain phase. The frequency of such symptoms could not be determined due to the scarce information available (only 2 studies).

Seven(25%) studies including 3810 patients described 41 non-migraine defining symptoms occurring in the headache phase of migraine attacks, most were migraine-related(blurred vision, dizziness, stiff neck or osmophobia). The most frequent occurring symptoms were cognitive, such as "impaired thinking", "feeling distracted or slow", and "speech difficulties", in line with previous studies suggesting the existence of attack-related cognitive dysfunction(108, 109).

Seven studies dwelt with the postdromes, including 1633 patients and describing 42 different symptoms, the majority migraine-related (including persistent mild pain in 36%). The most frequently reported symptoms were mood/behavioral changes, specially fatigue and/or tiredness, reported in all studies with frequencies varying from 52 to 88% (average 71%), depressive feelings (32%) and reduced physical energy(34%).

The present data supports that cognitive symptoms occur in all phases of the migraine attack, mostly affecting executive function (concentration difficulties, impaired thinking and slow processing) and language, a pattern consistent with evidence of attack related neuropsychological dysfunction(108, 109). Having migraine predicts limitations in cognitively demanding work(128); specifically, the migraine-attack associated concentration problems contribute to a perceived difficulty in handling the mental aspect of work during attacks, such as making decisions or performing out-of-the ordinary or complex work tasks. Patients also report more errors in tasks involving reading, writing, communication and arithmetic and the need to work in a slower pace. Mood changes, such as irritability, additionally limit patients' working abilities and interfere with interpersonal issues at work(93). Patients spontaneously discussing their experiences of migraine attacks in twitter report impact on productivity at work (3.5%) and school (2. 8%), but also in social life (3.5%) and specially in mood (43.9%)(129), maybe a reflection of persisting mood changes in the resolution phase.

There are a number of important limitations of this study findings, the first being that almost all studies were not controlled and data collection was not standard – most studies used clinical interviews and several different questionnaires, which induces an insurmountable bias on item selection and valorization. The statistical analysis performed in this review has low accuracy, it merely aimed to set and indicative proportion of symptoms to improve the qualitative analysis and should not be assumed at face value. The samples were mostly clinic-based but little information was available about migraine impact, recruiting was not homogeneous, as some studies included only aura patients, one studied only children and one only females. Another methodological limitations included the definition of each attack phase, that was not uniform between studies nor is there a consensus about their definition, some overlap being possible between phases. Also, the majority studies did not include information about the use of

preventives or acute attack treatments that could have concurrent symptoms by themselves. Adding to the potential reporting bias, not all the patients experience all phases of the attack and, in this review, symptoms described in different phases of the attack are also described by different patients, in different studies. One can even argue if patients noticing or not noticing prodromes and postdromes could represent a different subset of migraine patients- in Kelman series(23) they seem to be more sensitive to triggers, having longer duration of every phase of the migraine attack and have higher frequency of accompanying symptoms.

Conclusions

Due to the large number of included patients in this review, it is possible to assume that cognitive symptoms are consistently included in the description of the migraine attack phenomenology in published clinical series of migraine patients. Existing data also seems to support that cognitive symptoms are described in all phases of the attack, being the most frequent non-migraine defining symptoms reported in the prodromal phase and during headache. The cognitive symptoms most frequently described by patients are “concentration problems” in the premonitory phase and “impaired thinking” during headache. Concentration is also the most relevant cognitive complaint on the resolution phase of headache, but the most frequent non-migraine defining symptom of this phase is fatigue. Nevertheless, interpretation of this data is limited due to important methodological discrepancies and limitations of the evaluated studies.

Subjective Cognitive Symptoms during the Migraine attack.

A prospective study of a clinic based sample.

Gil-Gouveia R, Oliveira AG, Martins IP.

Subjective Cognitive Symptoms during the Migraine attack. A prospective study of a clinic based sample. Pain Physician 2016 *[in press];* Impact Factor: 4.77

ABSTRACT

The migraine attack is much more that a severe headache; it aggregates a range of different symptoms that contribute to attack-related disability. Cognitive dysfunction is an unacknowledged part of the migraine attack.

Our objective is to provide a profile of the frequency and character of migraine attack-related cognitive symptoms occurring specifically during the headache phase of the attack, by performing a cross-sectional systematic survey about cognitive symptoms in a clinical-based sample of episodic migraine patients, using an open-ended question followed by a self-fulfilled symptom checklist.

We studied 165 migraine patients (15 males, age average 37.3 ± 10.7 years), 87.3% of which spontaneously described cognitive symptoms occurring during the headache phase of the migraine attacks. On average 2.5 ± 1.6 symptoms were reported per patient, uninfluenced by demographic or disease-related variables. The most common spontaneous symptoms were within the executive domain, such as poor ability to concentrate (37%), difficulty in reasoning (25%) and thinking (23%). The pattern of responses on the symptoms checklist corroborated those reported spontaneously and quantitative scores of the checklist were higher in patients with spontaneous symptoms.

This study detailed the frequency and character of migraine attack-related subjective cognitive symptoms and found its frequency to be similar to reports of other migraine defining symptoms (ex. nausea, photophobia) in recent clinical series. Patients' reports were consistent and characterized by complaints of attention difficulties, diminished cognitive efficiency and processing speed impairment.

INTRODUCTION

The 2010 Global Burden of Disease study rates Migraine as the neurological disorder with the highest disability-adjusted life years (DALYs), being the seventh disabler worldwide(15, 130). In this study, the estimated disability of one day with a migraine attack was 43.3%(130); loss of effectiveness while at work reported by migraine patients varies amongst studies and countries, most commonly within the range of 40 to 50%(92).

Disability assessments on migraine rely on patients' self-report of ability to function during an attack. Some instruments also measure interictal burden, including limitations of work responsibilities and career progression, disruption of social and family interactions and ultimately health-related quality of life and comorbidities related to Migraine(131).

Ictal disability is assumed to be due to the pain and its impact has been measured using pain frequency, duration and intensity(131-136). During a migraine attack, pain is only a part of a constellation of symptoms and quite often patients report that their major cause of disability is not the pain itself, but other symptoms such as nausea and vomiting(133, 136-138), photophobia(137) or cognitive impairment(118).

Cognitive symptoms occurring during migraine attacks have been described since the first century(9); in more recent clinical series of migraine, cognitive symptoms described include not being able to think or concentrate (up to 71% of patients), being unable to carry out activities such as shopping(up to 83%), work or taking care of children(60%) contributing to migraine associated disability(95). However, cognitive dysfunction is far more often characterized in the premonitory(22-25, 27, 117) and posdromal phases(22, 25, 51, 52) of migraine.

In a previous study we conducted structured interviews about the occurrence of cognitive symptoms during migraine attacks, aiming to generate items for the development of an instrument to quantify subjective cognitive symptoms during attacks, the Mig-SCog(118). In the present study, using a similar methodology in a qualitative research study, we aim to detail the character and frequency of migraine attack-related subjective cognitive symptoms occurring in the headache phase of the attack in a clinic-

based sample of migraine patients. In addition, we want to determine if any demographic or disease related variable influenced the expression of such symptoms.

SUBJECTS and METHODS

Population

Volunteers were recruited from Headache Outpatient Clinics of two general hospitals in Lisbon, Portugal. Inclusion criteria were: a) age over 16 years old; b) at least two years of education (able to read and write); c) history of episodic migraine with or without typical aura, as defined by the ICDH-III(7);d) written informed consent of adult patients or of their legal guardians, in the case of patients aged 16 and 17. Because our focus was on cognitive symptomatology we excluded patients with chronic migraine, medication overuse and co-morbid mood disorders, factors potentially able to negatively influence cognition (89, 139). Non-typical auras and chronic tension-type headache were also exclusion criteria; episodic tension type-headache was allowed if the patient was able to distinguish between headache types. Previous history of alcohol or drug dependence or abuse or the presence of concomitant medical, neurologic or psychiatric disorders with influence on cognition were also exclusion criteria, as was pregnancy. The study protocol was approved by each Hospital's Institutional Review Board.

Study design

Recruitment and inclusion were carried out in a regular headache clinic visit along with standard clinical evaluation (detailed medical history, headache history, physical and neurological observation). After informed consent, a standardized data collection was performed, that included checking ICDH-III criteria and registering demographic and clinical details, such as gender, age, literacy, disease duration, current attack frequency, duration and intensity, attack and aura characterization, and detailed medical and pharmacological history. Migraine impact was evaluated with the HIT-6(140).

Data collection started with a closed question - “Do you feel any change of your mental abilities during the headache phase of your migraine attacks?” having a dichotomic (yes/no) answer. If the answer was affirmative, the researcher prompted the open-ended research question “please describe the main changes you usually feel” in order to elicit the spontaneous phrases or expressions that patients use to describe their experiences. Patients with aura were instructed to report only symptoms that occurred in attacks without aura or, if they had exclusively migraine with aura attacks, they were instructed to exclude symptoms that also started during the aura and persisted into the headache. All answers were recorded, irrespective of their content. All subjects had then to complete a self-administered symptom checklist of 43 items, including subjective cognitive (executive, spatial perception and language) and non-cognitive (mood, anxiety and visual) symptoms (118) which was used to confirm the preceding spontaneous symptom elicitations. Each item/symptom was rated qualitatively (yes/no) and on a 3-point scale - occurring often(2 points), rarely(1 point) or not occurring(0 points) during the attacks. A “don’t know, don’t want to answer” option was also available in order to avoid blank answers; if a blank answer was spotted upon checklist return the patients was prompted to complete it.

Data and Statistical Analyses

Answers to the open-ended question about cognitive symptoms were analyzed, classified and grouped into domains and functions by two authors (RGG, IPM) independently; discrepancies were resolved by consensus. Spontaneous symptoms were classified into non-cognitive and cognitive and then further classified into their specific domain (ex. executive, memory, language and others) and grouped into different functions within each domain (ex. initiative, processing speed etc.). The same process was applied to non-cognitive complaints, that were classified as mood-related, sensorial or migraine related, and groups into different symptoms (ex. mood, vision, phonophobia etc.). The number of different spontaneous symptoms was calculated for each domain, as was as the number of patients reporting each symptom, in order to obtain an average frequency of each symptom, in each domain. A frequency table was built including all cognitive and non-cognitive symptoms reported; the average number of symptoms per patient was calculated. Demographic and disease-related variables were compared

between patients with and without spontaneous cognitive symptoms with the chi-square test for proportions and Student's t-test for means.

Analysis of the symptom checklist excluded missing answers analysis-by-analysis ("don't know, don't want to answer"). Items were scored qualitatively (having/not having the symptom) and quantitatively (0 to 3) to analyze relative impact of each symptom. Checklist symptoms frequency derived from qualitative item scores. Quantitative items scores were used to calculate scores for each domain and for the total checklist. Linear regression analysis, using the total symptom checklist score as a dependent variable was performed to study the influence of demographic and disease-related variables.

Statistical analysis was made with SPSS v20.

RESULTS

1- Population

Total population had of 172 volunteers; seven were excluded due to medication overuse(n=5) or chronic tension-type headache(n=2). The study population consisted of 165 volunteers(15 males), nine left-handed, with an age average of 37.3 ± 10.7 years(range 16 to 63 years). Average disease duration was 20.5±12.2 years (range 6 months to 57 years), 25 patients had Migraine with aura(15.2%) and average HIT-6 Score was 61.2±7.3 (range 43 to 76).

Forty-one patients(29.7%) were on migraine prophylactics, most commonly on topiramate(11), propanolol(9), amitriptyline(7) and valproic acid(5) and flunarizine(2) or combinations. Attack treatment was based on triptans(33.4%), followed by analgesics(28.6%) and NSAIDs(28.5%) and ergots(9,0%). Twelve(7%) patients were taking low-dose anxiolytics or serotonin-specific reuptake inhibitors, 41(25%) were taking the combined oral contraceptive pill and 6(4%) were on hormone replacement therapy.

2.1 – Spontaneous cognitive symptoms

Seventeen patients(10.3%) did not feel any change of their mental abilities during the headache phase of their migraine attacks; the remaining 148(89.7%) patients reported on average 3.6±2.0 (range 1 to 9) different spontaneous subjective symptoms. These were classified as cognitive in 144(87.3%) patients, the average number of symptoms reported by patient being 2.5±1.6 (range 1 to 9, median of 2).

Table 1 – Spontaneous symptoms - Descriptive analysis

	SYMPTOMS			PATIENTS	
	Number of different symptoms	Number of reports	Average reports/ symptom	Patients with symptoms†	Number of symptoms/ patient‡
Cognitive	**54**	**416**	**7.7**	**144 (87%)**	**2. 5± 1.6 (0-9)**
Executive	31	297	9.6	132 (80%)	1. 7± 1.2 (0-5)
Language	9	52	5.8	42 (25%)	0. 3± 0.6 (0-3)
Memory	5	22	4.4	18 (11%)	0. 1± 0.4 (0-2)
Spatial perception	2	2	1	2 (1%)	0. 01± 0.1 (0-1)
Multi-domain	7	43	6.1	39 (24%)	0. 3± 0.5 (0-2)
Non-Cognitive	**32**	**188**	**5.9**	**97 (59%)**	**1. 1± 1.2 (0-5)**
Mood	9	69	7.7	54 (33%)	0. 4± 0.7 (0-3)
Sensorial	5	24	4.8	22 (13%)	0. 1± 0.4 (0-2)
Migraine	18	95	5.3	60 (36%)	0. 6± 0.9 (0-3)

The 148 patients reported the occurrence of 86 different symptoms during their headaches, using 604 different expressions to describe their symptoms. Fifty-four(62.7%) symptoms were cognitive– table 1.

The most frequent cognitive symptoms described related to executive dysfunction(71.4%), followed by language complains(12.5%). Non-cognitive symptoms were also frequent, mostly migraine related(50.5%) or mood changes(36.7%). Detailed

description of spontaneous symptoms is presented in tables 2 (cognitive) and 3 (non-cognitive).

None of the demographic variables (gender, age, literacy, disease duration, aura, previous diseases or current treatments, headache prophylaxis, attack treatment, attack frequency, intensity or duration and disease impact, measured by the HIT-6 score) influence the likelihood of reporting cognitive difficulties during migraine attacks.

Table 2 - Cognitive difficulties spontaneously reported in the headache phase of migraine attacks

	SYMPTOM DESCRIPTION	N	%
EXECUTIVE FUNCTION	**Low inhibitory control**	7	1.7%
	Lower tolerance / intolerant / grumpy	5	
	Can't stand the pain / unable to stop thinking about the pain	2	
	Avoidance	11	2.6%
	I want to be alone/ must be alone/ I want to isolate myself/ have to be in isolation	8	
	Difficulty in interaction with others / difficulty in social interaction / lower social abilities (friendliness and empathy)	3	
	Difficulty in maintaining attention	72	17.2%
	Difficulty or lack of attention / disperse / unable to focus or concentrate/ lower ability to concentrate/ worse concentration/ higher effort to achieve a minimum concentration level	61	
	Less attention/ distracted/ difficulty in paying attention/ difficulty in maintaining attention	8	
	Lose the notion of things / I feel the need to abstract from reality or not pay attention / I get abstracted / I feel lost in my thoughs	3	
	Cognitive Processing Efficiency/ Reasoning	99	23.8%
	Difficulty in reasoning / higher effort to reason / lower reasoning/ unable to reason / ineffective reasoning	41	
	Difficulty in thinking /I can't think/ lower ability to think/ thinking is effortful / I don't feel like thinking/ I'm not able to think straight / I have a hard time thinking /thinking is bothersome/ I can't think a long period of time/ I'm not able to think the same way as usual	38	
	Difficulty in making mental or intellectual effort/ intellectual laziness / mental fatigue/ I do not feel like thinking	4	
	I'm not able to have complex thoughts/ lower performance/lower work efficiency/ fear of failing more complex reasoning / less efficient flow of ideas / lower ability to process information	6	
	I get witless or rattle-brained / lower brain reflexes / rattle-headed/ brain blocked/ confused / incapable	10	
	Stamina	27	6.5%

	Tiredness/ more tired / exhausted	8	
	Less strength in all my body/ difficulty in standing up / less strength	3	
	Fell washed-out / I fell sluggish / without action / without energy / asthenia / globally indisposed	8	
	Lose all my abilities/ just exist / do not react, like a vegetable / get diminished / it feels like being anesthetized/ less reaction / I seem to be sedated/ get alienated of what is around me	8	
	Initiative	10	2.4%
	I don't feel like doing anything / unwilling / reluctant to do anything	3	
	Without initiative/ less predisposed to do things / lower motivation	3	
	Everything is done with effort /I have a hard time doing anything	4	
	Motor initiative and speed	8	1.9%
	Physical movement is difficult/ I cannot move/ unwilling to move	4	
	I walk slower and my movements are slower / moving is harder, slower and my body fells heavier/ slower movements, even when walking/ physically slower	4	
	Processing Speed	38	9.1%
	Slower thoughts/ need to think longer / slower reasoning / sluggish thinking	11	
	I fell slower or slowed/ slowness/ slowing/ lower speed/ idle/ slower reactions/ slower on chores	27	
	Planning	8	1.9%
	I have to write down everything I'll need to do/ have to plan with notes	2	
	Unable to organize daily chores/ I have a hard time organizing/ not able to program anything/ difficulty in planning ahead	6	
	Decision Making	9	2.2%
	Difficulty in decision taking/ difficulty in settling things/ less able to make a decision	4	
	Difficulty in getting things done / cannot execute things / not able to perform any chore / lower ability to act	5	
	Cognitive Flexibility	4	1.0%
	Difficulty in multitasking/ less able to pay attention to several simultaneous simple stimuli	2	
	Difficulty in solving practical problems/ difficulty in responding to stimuli or requests	2	
	Monitoring	1	0.2%
	Fear of making errors at work	1	
	Calculus	3	0.7%
	Difficulty in calculation or simple math's/ difficulty in sums, measurements, calculus	3	
	TOTAL EXECUTIVE	**297**	**71.4%**

MEMORY	**Learning**	7	1.7%
	Difficulty in memorizing/ difficulty in learning new information / difficulty in retaining information in a short period of time	3	
	I need more time to learn new things	1	
	Studying is difficult / the study is less productive	3	
	Retrieval	15	3.6%
	Memory lapses/ I forget thinks/ forgetful/ I fail to remember	9	
	My memory gets affected/ I get problems with my memory/ lack of memory/ damaged memory	6	
	TOTAL MEMORY	**22**	**5.3%**

LANGUAGE	**Naming**	2	0.5%
	Difficulty in speaking out people's names	1	
	I 'm not able to remember simples objects names	1	
	Speech Fluency	27	6.5%
	Difficulty in keeping a simple conversation/ difficult to chat/ cannot organize the sentences to speak properly/ I have a hard time programming what I want to say/ I'm not able to communicate/ I find it hard to explain what I mean, while talking	8	
	Difficulty talking/ not able to talk/ my speech gets stunted/ I have a hard time talking/ I feel the need to abbreviate all conversations	18	
	Difficulty in articulating the speech	1	
	Comprehension	7	1.7%
	Difficulty in understanding when being spoke to / It's hard to understand verbal information	5	
	Unable to pay attention to what's being asked / I'm not able to talk back when being spoke to	2	
	Reading and Writing	16	3.8%
	I cannot write, I forget how to write properly / I find it difficult to write/ writing takes longer than usual / I misspell more often when writing	5	
	Difficulty in reading/ difficulty in understanding what's written	11	
	TOTAL LANGUAGE	**52**	**12.5%**

OTHERS	**Spatial perception/ Topographic disorientation**	2	0.5%
	Pay less attention to normal paths or routes	1	
	Difficult to calculate distances	1	
	Difficulty in complex tasks (Multiple domains)	43	10.3%
	I'm not able to do anything/ completely disabled/ I get disabled/ I find it hard to do anything	9	

	I avoid to do any chore/ I avoid chores that have higher reasoning demands	2	
	Difficulty in household chores/ difficulty in everyday chores and routine activities/ I'm not able to do household chores	8	
	I can't work/ I'm not able to work properly	4	
	Difficulty in cooking	2	
	Difficulty in driving/ unable to drive	16	
	I do everything wrong/ I no longer know how to do anything	2	
	TOTAL OTHERS	**45**	**10.8%**

Table 3- Other differences (non-cognitive) of mental capacities spontaneously reported during the headache phase of migraine attacks

	SYMPTOM DESCRIPTION	N	%
MOOD CHANGES	**Depressed Mood**	7	3.7%
	Lowering of mood / changes in mood / sadness / tearfulness / will cry	6	
	Emotional fragility	1	
	Lower interest	31	16.5%
	Can't find patience to do anything / less patience /Lack of patience / impatience	30	
	Everything is bothersome	1	
	Anxiety	28	14.9%
	Irritable/ irritability	21	
	Anxious/ panic/ despair/ nervous / very nervous	5	
	Out of control/ upset	2	
	Nervous tension	3	1.6%
	Uptight/ tense	2	
	Need to relax	1	
	TOTAL MOOD	**69**	**36.7%**

SENSORIAL CHANGES	**Balance**	5	2,7%
	Disturbed by traveling	1	
	Stunned / Dizzy	2	
	Unbalanced and dizziness / I lose my balance while walking	2	
	Visual disturbances	17	9.0%
	Vision impairment / foggy vision /lack of sight /different or difficult vision/ I'm unable to see properly / difficulty in seeing / out-of-focus vision/ difficulty in far seeing	17	
	Sensitive disturbances	2	1.1%
	Slight hand numbness/ numb hand	2	
	TOTAL SENSORIAL CHANGES	**24**	**12.8%**

MIGRAINE RELATED	**Photophobia**	34	18.1%
	I need to get my eyes closed / difficulty in keeping the eyes open/I'm not able to open my eyes/ I cannot look at anything	8	
	Difficulty in watching television/ difficulty in staring at a computer screen/ Difficulty in making visual effort / I'm bothered by visual effort	11	
	I need to be in the dark / I cannot stand the light/ light worsens the pain/ I get photosensitive	15	
	Phonophobia	27	14.4%
	I need to be in a quiet room/ It's hard for me to hear any noise/ noise disrupts my concentration	10	
	I lack the patience to listen to anything/ I can't hear anything or anybody/ lower tolerance to noise/ I'm bothered by noises/ the sound of my own speech is distressful	11	
	Difficulty listening/ Cannot listen/ I have a hard time listening to what people say/ the sounds seem far away	6	
	Kinesiophobia	19	10.1%
	Difficulty walking/ I have a hard time walking	5	
	My wish is to be still / I need to stay still	2	
	I feel like lying down/ I urge to lie down/ I need to rest still/ I cannot wait to go to bed	7	
	Difficulty in climbing stairs/ Physical effort is difficult/ I'm not able to make any effort/ Cannot pick up any weight	4	
	Difficulty in turning my head	1	
	Osmophobia	2	1.1%
	Can't stand any smell or odor	2	
	Gastrointestinal upset	3	1.6%
	I get nauseated / Bothersome nausea	2	
	I can't eat/ I get stuffed without eating	1	
	Sleep disturbances	7	3.7%
	Not able to sleep	2	
	Sleepiness / too sleepy	5	
	Others	3	1.6%
	I get haggard / I get pale with dark circles around the eyes	2	
	I need to squeeze my head	1	
	TOTAL MIGRAINE RELATED	**95**	**50.5%**

2.2 – Symptom checklist

Most of the items of the symptom checklist had less than 10% missing values ("do not know, don't want to answer"), exceptions were: difficulty in drawing(59% missing), in naming famous people(19%), in mental calculus(13%), in writing(11%) and about right/left orientation(10%). All the items of the symptom checklist had at least one positive answer. Positive answers were extremely frequent (> 90%) in only 3 items: attention *(…do you have trouble concentrating?*, 93%), stamina (*… do you feel tired?*, 91%)

and anxiety (*…do you feel irritable?*, 90%). Answers were very frequent (>80%) in items of motor initiative and processing speed (88%), attention, cognitive flexibility, cognitive processing efficiency and motor processing speed(85%); non-cognitive very frequent answers included anxiety(84%) and visual symptoms (82%). Complete description of the symptom checklist answers is available (table 4).

None of the demographic variables (gender, age, literacy, disease duration, aura, previous diseases or current treatments, headache prophylaxis, attack treatment, attack frequency, intensity or duration and disease impact using HIT-6) had influence on the total score of the symptoms checklist that was used as the dependent variable in a linear regression analysis.

Table 4 –Scores of the symptom checklist, per item

During your headache…

		Yes	M	% (%)	Av ± SD
EXECUTIVE FUNCTION	**Attention**	**132**		**80%**	
	…do you have trouble concentrating?	154	0	93%	1.5 ± 0.6
	…do you find it difficult to follow or maintain attention when being spoken to?	140	0	85%	1.2 ± 0.7
	… are you easily distracted?	103	7	62 (65)%	1.0 ± 0.8
	Stamina	**150**		**91%**	
	… do you feel tired?	150	1	91 (91)%	1.5 ± 0.6
	Initiative	**94**		**57%**	
	… do you have trouble starting an activity ?	128	8	78 (81)%	1.2 ± 0.7
	… do you have trouble in taking initiative?	118	6	72 (74)%	1.0 ± 0.7
	… do you forget to take your pain-killers?	36	3	22 (22)%	0.3 ± 0.6
	Motor initiative and speed	**146**		**88%**	
	… do you have trouble performing tasks at your normal speed?	146	1	88 (89)%	1.4 ± 0.7
	Planning	**112**		**68%**	
	… do you have trouble in remembering about things you need to do (e.g. paying bills, making phone calls etc.)?	105	6	64 (66)%	1.0 ± 0.8
	… do you find it hard to plan your routine chores (e.g. cooking, shopping etc.) and compromises?	120	11	73 (78)%	1.1 ± 0.7
	Cognitive Flexibility	**118**		**72%**	
	… are you able to deal with several stimuli at the same time (ex to be able to drive)?	141	5	85 (88)%	1.0 ± 0.8
	… do you find it difficult to change your activity?	95	12	58 (62)%	0.8 ± 0.8
	Monitoring	**53**		**32%**	
	… do you lose the correct notion of time?	53	7	32 (34)%	0.4 ± 0.6
	Cognitive processing efficiency / Reasoning	**124**		**75%**	
	… do you have trouble thinking?	125	1	76 (76)%	1.1 ± 0.8
	… do you have trouble maintaining the tread of your thoughts?	141	2	85 (86)%	1.3 ± 0.7

	...do you feel confused?	107	2	65 (66)%	0.8 ± 0.7
	Processing speed	**143**		**87%**	
	… do you find it difficult to think at your normal speed?	146	1	88 (89)%	1.4 ± 0.7
	… do you find it difficult to react at your normal speed?	140	5	85 (88)%	1.4 ± 0.7
	Calculus	**118**		**72%**	
	… do you find it difficult to do mental calculation?	118	21	72 (82)%	1.2 ± 0.7

LANGUAGE	**Naming**	**57**		**35%**	
	… do you have trouble speaking out other people's names?	78	1	47 (48)%	0.6 ± 0.8
	… do you have trouble in remembering objects names?	65	2	39 (40)%	0.5 ± 0.7
	… do you have trouble in memorizing people's names?	68	9	41 (44)%	0.6 ± 0.8
	… do you have trouble recognizing famous people?	16	32	10 (12)%	0.2 ± 0.4
	Comprehension	**87**		**53%**	
	… do you have trouble in understanding when being spoke to?	87	2	53 (53)%	0.8 ± 0.8
	Speech Fluency	**83**		**50%**	
	… do you have trouble in organizing your ideas in order to speak correctly?	97	5	59 (61)%	0.8 ± 0.8
	… do you speak with a lot of interruptions or brakes?	108	4	65 (67)%	1.0 ± 0.8
	… do you switch the words you want to speak by others?	71	7	43 (45)%	0.6 ± 0.7
	… do you switch the sounds or syllables within words ?	50	10	30 (32)%	0.4 ± 0.7
	… is your voice slurred when speaking?	71	9	43 (46)%	0.6 ± 0.8
	… do you have difficulty in organizing a sentence or a conversation?	99	1	60 (60)%	0.9 ± 0.8
	Reading and Writing	**102**		**62%**	
	… do you have trouble writing?	82	18	50 (56)%	0.8 ± 0.8
	… do you find it difficult to read?	121	11	73 (79)%	1.3 ± 0.8

OTHER	**Spatial Perception**	**47**		**28%**	
	… do you fell disoriented in a familiar place?	48	1	29 (29)%	0.4 ± 0.6
	… do you find it difficult to draw?	29	98	18 (43)%	0.6 ± 0.7
	… do you confuse left with right?	26	16	16 (17)%	0.2 ± 0.6
	… do you have trouble following a route (by driving or walking)?	85	3	52 (52)%	0.7 ± 0.7

NON-COGNITIVE	**Mood Changes**	**82**		**50%**	
	… do you feel like crying?	104	2	63 (64)%	1.0 ± 0.8
	… do you feel sad?	130	4	79 (81)%	1.2 ± 0.8
	… do you feel euphoric or pleased?	11	9	7 (7)%	0.1 ± 0.3
	Anxiety	**143**		**87%**	
	… do you feel irritable?	148	0	90%	1.4 ± 0.7
	… do you feel nervous or anxious ?	138	2	84 (85)%	1.3 ± 0.7
	Visual Symptoms	**111**		**67%**	
	… do you have staring?	136	3	82 (84)%	1.4 ± 0.8
	… does your vision feels foggy?	87	1	53 (53)%	0.7 ± 0.8

The most frequent cognitive symptoms identified in the symptoms checklist were executive, followed by language and spatial perception, having a distribution per domain that was comparable to that of the spontaneous symptoms (table 5).

Table 5 – Spontaneous and symptom checklist symptoms per domain

	Spontaneous Symptoms frequency	Symptom checklist frequency	Number of spontaneous symptoms/ patient	Symptom checklist score
Total	**148 (90%)**	**165(100%)**	**3. 6± 2.0**	**35.9 ± 15.6**
Cognitive	**144 (87%)**	**83 (50%)**	**2. 5± 1.6**	**30.4 ± 13.6**
Executive	132 (80%)	119 (72%)	1. 7± 1.2	20. 2± 7.7
Language	42 (25%)	82 (50%)	0. 3± 0.6	8.8 ± 6.0
Spatial percep.	2 (1%)	47 (28%)	0. 01± 0.1	1. 5 ± 1.5
Non-Cognitive	**97 (59%)**	**112 (68%)**	**1. 1± 1.2**	**7. 1± 3.0**
Mood	54 (33%)	112 (68%)	0. 4± 0.7	5.0± 2.3
Sensorial	22 (13%)	111 (68%)	0. 1± 0.4	2. 1± 1.3

Non-cognitive symptoms, classified in mood-related or sensorial, showed identical frequency when classified by the symptom checklist, but mood-related complaints were proportionally more frequent than sensorial symptoms when answering to the open-ended research question (table 5).

Table 6 – Checklist scores in patients with and without spontaneous symptoms

	Spontaneous Symptoms (all)		p	Spontaneous Symptoms (cognitive)		p
	No	Yes		No	Yes	
SYMPTOM CHECKLIST	17	148	--	21	144	--
Total	22.7 ± 15.0	39.2 ± 14.8	<0.0001	24.1 ± 14.3	39.5 ± 14.8	<0.0001
Cognitive	18.0 ± 12.8	31.9 ± 13.1	<0.0001	19.0 ± 12.4	32.1 ± 13.1	<0.0001
Executive	12.4 ± 7.4	21.1 ± 7.2	<0.0001	13.0 ± 7.1	21.2 ± 7.2	<0.0001
Language	4.7 ± 4.6	9.2 ± 6.0	0.001	4.8 ± 4.7	9.3 ± 6.0	0.001
Spatial perception	0.9 ± 1.3	1.5 ± 1.5	0.119	1.1 ± 1.2	1.5 ± 1.6	0.206

Non-Cognitive	4.6 ± 3.3	7.3 ± 2.9	<0.0001	5.1 ± 3.4	7.3 ± 2.9	0.002
Mood	3.5 ± 2.2	5.2 ± 2.2	0.004	3.8 ± 2.3	5.2 ± 2.2	0.011
Sensorial	1.2 ± 1.2	2.2 ± 1.2	0.002	1.3 ± 1.3	2.2 ± 1.2	0.004

Quantitative scores on the symptoms checklist were higher in patients spontaneously reporting symptoms in the open-ended question (table 6).

DISCUSSION

In this study we screened for the frequency subjective cognitive symptoms occurring during the headache phase of migraine attacks. Cognitive complaints were found to be very common in this setting; we were able to provide an extensive description of symptoms using patients' phraseologies in order to help clinicians to recognize their usual pattern. The consistency of our findings supports patients' spontaneous claims of cognitive impairment during attacks, These symptoms probably contribute to the self-perceived decrease of 64% in work efficiency during attacks(92) and to migraine related disability and burden; their identification allows to improve the perception of patients' impairment and the adequacy of treatment strategies.

The majority (87.3%) of episodic migraine patients report cognitive symptoms during attacks, a percentage comparable to reports of nausea(52-86%), photophobia(55-80%), phonophobia(47 to 100%) and pain aggravation by physical effort (53-70%) in large clinical series of migraine(17, 18, 44, 141), supporting that cognitive symptoms are an intrinsic part of the attack(118). Analysis of prodromal and postdromal cognitive symptoms' incidence is around 20 and 30% respectively, comparable to reports of photophobia (21 and 18%), phonophobia (21 and 15 %) and nausea (23 and 11%) in the same attack phases(22-25, 52, 54).

Non-cognitive symptoms included in the answers to our study question were either attack-related (such as photophobia, phonophobia, gastrointestinal upset, etc), accompanying mood changes (anxiety, depressed mood, etc) or sensorial complaints (balance, visual and sensitive disturbances), all described in clinical series of migraine patients(20, 43, 44). These were unanticipated answers, as often occurs with open-ended questions. To our purpose of surveying the maximum variety of spontaneous

cognitive symptoms without influencing or leading the answers, an open-ended question was more likely to provide in-depth information, while assuming the risk of over-interpretation of the term "*mental abilities*". The fact that <u>*all*</u> non-cognitive symptoms reported were migraine-related can be valued as a concurrent validity measure, implying that patients' answers were strictly referring to phenomena occurring during migraine attacks.

On average, 2.5 cognitive symptoms were reported spontaneously by each patient, which can be explained either by the high frequency of different symptoms but most likely by the difficulty in describing the symptomatology; 92% of patients reported 1 to 4 symptoms. Cognitive difficulties are often vague and difficult to define either because its experience may not be universal or they may be influenced by performance of complex tasks involving several cognitive domains. To support this view, 24% of patients reported difficulties in complex tasks, such as cooking, driving or everyday tasks, being unable to define what the specific difficulties of task execution were.

We were unable to find a relation between the presence of cognitive symptoms during attacks and any of the demographic or migraine related variables, nor to migraine impact.

Variables that were expected to influence the report of subjective cognitive complaints include psychological disturbances (depression, chronic stress/exhaustion and sleeping problems(142)), the female gender (especially during pregnancy(143) or menopause(144)), medication (including migraine prophylactics, antidepressants and hormones)(145-147) and age(81).

Our study design limited the influence of some of these variables, as we excluded co-morbid mood disorders and pregnancy. We were unable to find any effect of age in the frequency of spontaneous symptoms or in the score of the symptoms checklist, probably reflecting the young age average of our population, typical of migraine patients. Our sample had a low percentage of patients on prophylactic treatment (under one third), 42% of which were using topiramate, a drug that influences cognitive functioning(145). We were unable to find any relation of topiramate use to the number of spontaneous cognitive symptoms nor to the score of the symptoms checklist. Around 7% of our subjects were taking low-dose anxiolytics or serotonin-specific reuptake inhibitors and

4% were post-menopausal women on hormone replacement therapy, however our data did not allow us to determine any effect of these variables.

The lack of association of cognitive symptoms to migraine disease duration or impact suggests that cognitive dysfunction in episodic migraine is mainly an attack-related phenomena and perception of cognitive decline is not a consequence of migraine, by itself(104). This assumption requires confirmation in further studies powered to answer this question.

There were three symptoms very consistently described by patients using a very similar phraseology, the first being a lower ability to concentrate (14.7% of symptoms, reported by 37% of patients), followed by difficulty in reasoning (9.8% of symptoms, 25% patients) and being "less able" to think (9.1% of symptoms, 23% patients), reflecting attention and cognitive processing efficiency problems. Symptoms that could be attributed to executive domains comprised about 2/3 of spontaneous complaints, probably relating to their relevance in daily functioning compared to other domains (E.g. impaired drawing ability). The symptom checklist also screened infrequent cognitive activities; difficulties in determining some symptoms' occurrence were reflected in high percentages of missing answers of some items – 59% patients were unable to say if they had drawing difficulties, 19% did not know if it was hard to recognize famous personalities and 13% if their mental calculus was appropriate, during attacks. Average scores on the symptom checklist were lower in patients without spontaneous symptoms. The differences between spontaneous or cued reporting can be due to lower impact of these symptoms or to differences in metacognition abilities of some individuals.

The pattern of spontaneous cognitive symptoms identified is consistent to previous descriptions of difficulties during attacks(9, 11, 95), with descriptions of prodromal and postdromal symptoms(22-25, 52, 54) and to objective impairment, as identified by neuropsychological testing during attacks(108, 109) most consistently in domains of attention, processing speed, working memory and learning. Language related symptoms were also frequent, while memory complaints were not as usual.

It remains speculative why this specific pattern emerges during attacks and even putting aside the discussion if these subjective symptoms relate to clinically relevant brain dysfunction, their consistency supports that these brain functions are modified during migraine attacks. Attention, processing speed and working memory have some

common characteristics, namely (1) being basic executive functions, related to pre-frontal activity; (2) representing brain processes that subserve other higher-order cognitive domains and (3) depending on subcortical circuitry.

Attention may be viewed as brain network function involving three subsystems – alertness or arousal (thalamic function), orienting or selection (parietal function) and executive or conflict resolution (anterior cingulated function) that might interact or function independently(148). Processing speed is influenced by subcortical white matter(149) and/or cortical structures(150). Working memory is a prefrontal cortex function that involves different areas according to the specific task required; recent evidence suggests that dorsal prefrontal cortex plays a more prominent role in encoding information while retrieval may be mediated either by the ventral or the dorsal prefrontal cortex(151).

The participation of cortical brain areas in migraine attacks has been documented for in the insula, temporal lobe(152) and cingulated and pre-frontal cortex(153). Subcortical structures, such as the raphe nuclei with its cortical serotoninergic projections (ex. orbitofrontal cortex, precentral gyrus, temporal pole, insula and somatosensory area)(154) and the thalamus are also activated during attacks in humans(153) and may represent the anatomical substrate explaining this symptomatology. Improving the knowledge about cognitive dysfunction during migraine attacks can provide clues to the brain processes occurring within the attack and help in determining the sequence of brain events resulting in the episodic dysfunction of migraine patients.

We acknowledge that the frequency of cognitive symptoms occurrence is probably overestimated in our study, as the research question was open-ended and interview based, which may incite the patient to respond affirmatively. We could have chosen to use a standard research method in issue exploration, such as the modified Delphi technique, that would have had the advantage of improving the consensus over which symptoms would be relevant in this context and increase accuracy of results. However, it has several potential disadvantages such as higher work load, the potential of low response rates and for molding opinions by investigators and the risk of reducing variability(155). Our priority was to be as inclusive as possible, to identify the maximum

variety of spontaneous cognitive symptoms without influencing or leading the answers and we wished to provide clinicians the expressions most often used by patients.

We chose a clinic-based population with episodic migraine, excluding severe co-morbid mood disorders, chronic migraine and medication overuse because we wanted to focus on the attack and avoid potential confounding factors on cognition (89, 139). As a consequence, our results cannot be extrapolated for the general population, but are probably useful in neurology and headache clinics. Medication use is an important potential confounder not controlled for and acknowledged as a limitation of this study.

We conclude that reversible subjective cognitive symptoms are consistently described in the headache phase of the migraine attack. The pattern most often reported (either by its frequency or by its relevance on functional ability) is of attention, cognitive efficiency and speed impairment, probably relating to pre-frontal or, most likely, subcortical brain networking dysfunction. Migraine attacks are the hallmark of Migraine as a disease; further knowledge about brain function during these events may help to identify new therapeutic targets or developing therapeutic agents in which efficiency would not be restricted to the control of pain, but also to attack-related reversible cognitive symptoms.

The impact of cognitive symptoms on migraine attack-related disability.

Gil-Gouveia R, Oliveira AG, Martins IP.
The impact of cognitive symptoms on migraine attack-related disability.
Cephalalgia 2015 *[e-pub ahead of print];* Impact Factor: 4.12;

ABSTRACT

Background: The socio-economic impact of Migraine is mostly related to work loss either by absenteeism or decreased work performance. Migraine associated cognitive dysfunction during an attack may contribute to these difficulties.

Objective: To analyze the presence and relevance of cognitive symptoms during migraine attacks and to relate their intensity and symptom related disability with other migraine defining symptoms.

Methods: Consecutive migraine patients of headache clinic completed diaries scoring each migraine symptom (including cognitive symptoms) intensity and symptom related disability.

Results: Of 100 consecutive patients included in this study, 34 (all females, age average 31.8±8.8 years) returned information on 229 attacks, on average 6.7 per participant. Every symptom's intensity was always rated slightly higher than the disability it caused. Pain was the symptom scored with the highest intensity and disability, followed by cognitive symptoms (difficulty in thinking and worsening with mental effort) and photo and phonophobia. Scoring was independent of any of the clinical variable. Attack intensity and disability scores correlated with intensity and disability from pain and from worsening with mental effort.

Conclusions: Attack-related cognitive symptoms are intense and disabling. Intensity and disability subjectively attributed to some attack-related cognitive symptoms correlate to intensity and disability subjectively attributed to the migraine attack. New acute migraine drugs trials should include cognitive evaluation as a secondary end-point, in order to be able to diminish decreased work performance and Migraine burden.

INTRODUCTION

Cognitive symptoms, although reported frequently by patients during migraine attacks (22, 54, 95, 118, 133, 136, 156) are not considered as core symptoms of the migraine diagnosis(7). Patients self-report being only 46% effective when working during migraine(92), but which part of this disability is related to cognitive dysfunction is undetermined.

Cognitive symptoms often precede migraine attacks, being very frequent in the premonitory phase of migraine(23, 25, 157) and having a high predictability for an attack (22). Disturbances of speech or thought are also described in the time gap between the end of the aura and the onset of pain (42). Cognitive difficulties can persist after the headache phase as postdromes (22, 25, 51, 54, 157) and may not be relieved by acute migraine medication (95, 158). Cognitive symptoms are not a usual endpoint of acute treatment trials in migraine.

Cognitive dysfunction during migraine has been documented in some studies(98, 100, 102, 109, 159), with involvement of the domains of processing speed(109), working memory, visual-spatial processing(98, 102, 159), immediate and sustained attention and verbal learning(100, 109). This is suggestive of preferential dysfunction of the pre-frontal and temporal cortices during migraine attacks.

These migraine-related clinical manifestations on cognition are important evidence of functional brain changes underling migraine pathophysiology and should be appointed as a therapeutic targets to be dealt with when evaluating acute treatment drugs.

Our objective was to analyze the presence and subjective relevance of cognitive symptoms during migraine attacks, by collecting data prospectively on paper diaries regarding the intensity and disability of cognitive and migraine-defining symptoms(7) in each attack of migraine patients.

SUBJECTS and METHODS

1. Population

Participants were recruited consecutively on a Headache Outpatient Clinic, either first or follow up visits during the first semester of 2013 and invited to participate. Inclusion criteria were: a) age between 18 and 55 years; b) minimum education of nine years; c) minimum headache frequency of one monthly attack in the 3 months preceding inclusion; d) written informed consent; e) diagnosis of definite episodic migraine with or without aura according to ICDH-II(13)

Exclusion criteria were simultaneous presence of migraine (either with or without aura) and other headache types that could present with attack-related or nonattack-related cognitive symptoms, including tension-type headache, chronic migraine with or without medication overuse and migraine aura without headache. A history of past or current alcohol or drug dependence or abuse and the presence of severe or uncontrolled medical or psychiatric disorder were also exclusion factors. The study protocol was approved by the Institution's Review Board.

2. Study design

Recruitment and inclusion were carried out by a headache specialist at a regular clinic visit who verified the patient eligibility criteria and carried out a standard clinical evaluation. After informed consent had been obtained, data was collected including verification of ICDH-II criteria for diagnosis, gender, age, literacy, disease duration, current attack frequency, duration and intensity , attack and aura characterization, use of prophylactic treatment and detailed medical and pharmacological history. At the end of the routine appointment, the patient was asked to complete the Mig-SCog(118) and HIT-6(140) scales. The Mig-SCog(118) is a 9-item questionnaire that quantifies self-reported subjective cognitive symptoms during migraine attacks and its score can run from 0 to 18, the higher scores representing higher frequency of cognitive symptoms; the HIT-6 (140) is a 6-item standardized questionnaire that measures the impact of migraine on functional status and well-being. Patients were also given 10 headache diaries, one for each migraine attack, including information about timing of the attack (start and end of pain, timing of medication and of completion of the diary), medication use (acute and rescue medication) and about intensity and disability related to each attack. Attack treatments were grouped into 5 categories: Triptans, NSAIDs, Analgesics

(including combination analgesics with codeine, caffeine or ergots) and Anti-emetic drugs in combination (either with triptan, NSAID or analgesic). On one side of the sheet, patients were asked to rate each migraine symptom's intensity on 0-10 visual analog scale (VAS), for that specific migraine attack (intensity of pain, nausea, photophobia, phonophobia, kinesiophobia(45), worsening with physical effort, worsening with mental effort, difficulty in thinking and global attack intensity). On the reverse side of the sheet, patients were asked to rate each migraine symptom related disability on 0-10 VAS scale, for that specific migraine attack (disability attributed to pain, nausea, photophobia, phonophobia, kinesiophobia(45), worsening with physical effort, worsening with mental effort, difficulty in thinking and global attack disability).

Diaries were returned on follow up appointments occurring before the 31st December 2013.

3. Statistical Analyses

Statistical analysis used Stata release 12 (Stata Corp., College Station, TX). Generalized Estimating Equation (GEE) with gamma family and a log link, with an AR(1) correlation structure and robust standard errors based on the Huber-White-sandwich variance estimator was used to analyze the relationships between scores of the different migraine symptoms adjusted by all other symptoms. A correlation coefficient between scores of any two symptoms was obtained with Spearman's rank correlation after averaging each patient's symptom scores over all the episodes. GEE analyses using global attack intensity and global attack related disability as the dependent variables were performed. Significance was set at the 5% level ($p < 0.05$). The Holm-Bonferroni procedure was used to correct p-values for multiple testing.

RESULTS

1.1 Population

One hundred patients were included in this study, eight males, with an age average of 31.2 ± 7.5 years, of whom 13 had migraine with aura and 87 without aura. There were 9 (14%) dropouts for several reasons (losing their diaries, forgetting to bring the diary in the scheduled follow-up, not having had time to fulfill the diaries or returning very

incomplete diaries that were not included; one patient emigrated); 57 patients failed to attend the scheduled follow-up.

Thirty-four patients returned 229 impact diaries, an average of 6.7 ± 3.0 (range 1 to 10) per participant. Patients not returning their diaries were similar in their demography and headache characteristics to participants (table 1) but were excluded from further analysis.

Table 1 - Clinical Characteristics of participants and non-participants

	Non-participating Patients	Participating Patients	p
Total Number	66	34	--
Gender (Female : Male)	58 : 8	34 : 0	n.s.
Age (years, average ± sd)	30.9 ± 6.8	31.9 ± 8.8	n.s.
Literacy (years, average ± sd)	14.8 ± 1.5	15.4 ± 1.3	n.s.
Associated Diseases (yes : no)	19 : 47	11 : 23	n.s.
Migraine (with : without aura)	8 : 58	7 : 27	n.s.
Disease Duration (years, average ± sd)	15.1 ± 9.2	15.4 ± 9.7	n.s.
Attack frequency (monthly, average ± sd)	5.1 ± 4.8	5.8 ± 5.2	n.s.
Preventive Medication (yes : no)	25 : 41	13 : 21	n.s.
HIT- 6 (score, average ± sd)	62.9 ± 4.2	63.4 ± 4.4	n.s.
Mig-SCog (score, average ± sd)	7.6 ± 4.1	8.6 ± 4.1	n.s.

Legend: sd – standard deviation; n.s. non-significant, p> 0.010

The study sample consisted of 34 females, one left-handed, of whom 6 had migraine with aura and 28 without aura, with an age average of 31.8 ± 8.8 years. Average HIT-6 Score was 63.4 ± 4.4 (range 50 to 70), reflecting a moderate to severe impact of migraine although 68% of the sample had 5 or less headache days in the month preceding inclusion. Mig-SCog Score average was 8.6 ± 4.1 (range 2 to 18), a medium score of subjective cognitive complaints.

Medical co-morbidities were present in 11 (32%) patients, mostly vascular risk factors (high cholesterol and obesity, 2 patients each), followed by thyroid dysfunction (2), asthma or allergies (2), mild anxiety or depression (2) and others (congenital glaucoma and esophageal reflux or gastritis). Twenty (67%) of these patients were on

birth control methods (19 oral contraception, 1 local hormonal devices) and 13 (43%) on prophylactic headache treatment (amitriptyline 2, topiramate 6, propranolol 3, valproid acid 2). Five (15%) patients were on other medical treatments (lower dose SSRI antidepressants 2, asthma treatment, thyroid hormone, statin and topic glaucoma treatment, 1 patient each).

Headache diaries were completed on average 14.2 ± 7.5 hours (range 4.1 to 26.4) after the end of each attack. The average time interval from inclusion to handing back of the diaries was 96.1 ± 64.2 days (range 19 to 270 days, 8.8 months).

1.2 Migraine attack characteristics

Average duration of the studied attacks was 20.0 ± 14.3 hours (range 4.2 to 67.2 hours). Analyzing attack clinical features, 207 (90.4%) fulfilled the ICDH-II criteria for migraine, 19 (8.3%) for probable migraine and only 2 (0.9%) could be classified as probable tension-type headache. On average, patients waited 3.0 ± 4.5 hours (range 5 minutes to 20 hours and 45 minutes) before taking their acute medication.

All the patients took acute medication in at least one of their attacks; most of the patients (18, 52.9%) took it in all reported attacks and twelve (25%) took it in more than 2/3 of attacks.

Of the 229 attacks studied, 221 (96.5%) were treated. The first choice of abortive treatment in this sample were triptans (48.4% of treated attacks), either alone (38.5%) or in combination with an anti-emetic drug (5.9%) or with an NSAID (4.1%). NSAIDs were the second choice in 40.7% of patients (alone 29.9% or with an anti-emetic 6.8%). Analgesics, combination analgesics with codeine, caffeine or ergots were used in 9% of attacks, in 1.8% adding an anti-emetic.

Rescue medication was used in 45.7% (101) of initially treated attacks and taken on average 4.5 ± 5.2 hours (range 15 minutes to 20.5 hours) after the initial therapy. The first choice of rescue treatment were NSAIDs (43.6%, with 5% adding an anti-emetic and 5.9% a triptan). Triptans were chosen secondly as rescue therapy by 35.6%, adding an anti-emetic in 3.0%.Thirteen percent of attacks required repeated

rescue medication. Analgesics, combination analgesics with codeine, caffeine or ergots represented the choice in 10.9% of attacks, in 1% adding an anti-emetic.

1.3 Symptom Intensity and Disability

Results of scoring symptom intensity and symptom-related disability on a 0-10 VAS scale are depicted in table 2. Intensity was rated slightly higher than disability, in all symptoms. Pain was the symptom with higher intensity and disability, followed by cognitive symptoms (difficulty in thinking and worsening with mental effort) and photo and phonophobia.

Table 2 - Average Scores of Symptom Intensity and Symptom related Disability

	Intensity (0-10 VAS)		**Disability (0-10 VAS)**	
	Average ± SD	Range	Average ± SD	Range
Global – of the Attack	5.5 ± 2.1	0.9 - 10	4.2 ± 2.0	0 – 9.3
Pain	6.0 ± 1.8	1.7 -10	5.2 ± 2.2	0.7 -9.9
Nausea	3.2 ± 2.1	0 – 8.6	2.5 ± 2.1	0 – 8.6
Photophobia	4.4 ± 2.3	0.4 – 9.6	3.5 ± 2.6	0 – 9.6
Phonophobia	4.3 ± 2.3	0.3 – 10	3.5 ± 2.6	0 – 9.4
Kinesiophobia	4.0 ± 2.0	0 – 8.6	3.2 ± 2.2	0 – 8.7
Worsening with Physical Effort	4.2 ± 2.1	0 – 9	3.6 ± 2.2	0 – 8.6
Worsening with Mental Effort	4.9 ± 2.0	0.4 – 9	4.1 ± 2.2	0 – 8.8
Difficulty in thinking	4.8 ± 2.1	0.3 – 9	4.1 ± 2.2	0 – 8.8

1.4 Correlations and Regression Analysis

Age was found to correlate with disease duration (Spearman's rho 0.659, $p<0.0001$) and inversely with attack frequency (Spearman's Rho -0.475, $p=0.005$). Reported attack duration correlated with time to take rescue medication (Spearman Rho 0.645, $p<0.0001$) after initial acute treatment, but not with time to take initial acute treatment. There were no other significant correlations between disease related variables (age, literacy, disease duration, attack frequency, reported attack duration and number of attacks reported, HIT-6 and Mig-SCog scores).

Correlation coefficients between using each type of acute medication and intensity and disability of cognitive symptoms (worsening with mental effort and difficulty in

thinking) are depicted in table 3; Intensity of cognitive symptoms was correlated with the use of triptans or analgesics as first choice in rescue treatment; disability of cognitive symptoms related to all drug groups except anti-emetics in combination with any other drug. . Intensity and disability of cognitive symptoms had no correlation to the need of rescue treatment.

Table 3 - Initial acute treatment correlations with attack-related cognitive symptoms

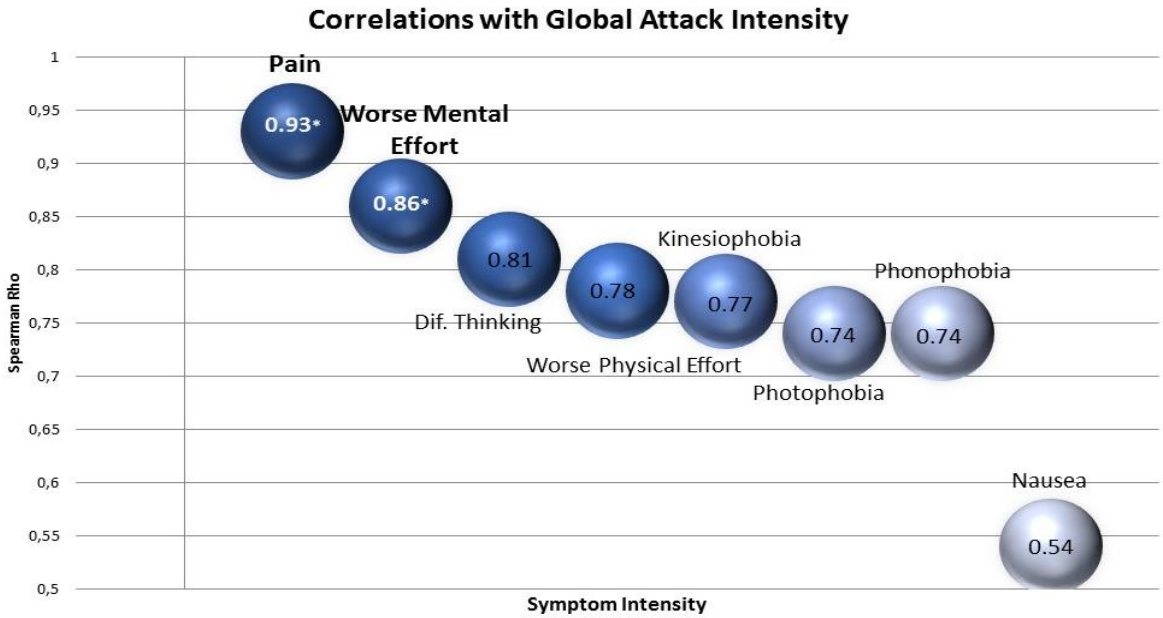
		Spearman Correlation Coefficient	95% Confidence interval		p-value
Intensity of worsening with mental effort	Triptans	0,396	0,163	0,630	0,001*
	NSAIDs	0,138	-0,018	0,294	0,083
	Analgesics	0,539	0,228	0,851	0,001*
	Anti-emetic drugs plus	0,082	-0,157	0,320	0,502
Disability of worsening with mental effort	Triptans	0,653	0,293	1,012	<0,0001*
	NSAIDs	0,427	0,201	0,652	<0,0001*
	Analgesics	0,847	0,536	1,157	<0,0001*
	Anti-emetic drugs plus	0,217	-0,161	0,594	0,261
Intensity of difficulty in thinking	Triptans	0,433	0,112	0,754	0,008*
	NSAIDs	0,198	-0,024	0,420	0,081
	Analgesics	0,661	0,178	1,144	0,007*
	Anti-emetic drugs plus	0,083	-0,210	0,376	0,578
Disability of difficulty in thinking	Triptans	0,627	0,261	0,992	0,001*
	NSAIDs	0,359	0,116	0,602	0,004*
	Analgesics	0,775	0,429	1,120	<0,0001*
	Anti-emetic drugs plus	0,227	-0,117	0,570	0,196

Legend: significant correlation, p< 0.010

Correlations found between intensities of each migraine symptom were scarce – intensity of pain only correlated with intensity of worsening with mental effort (p=0.02), intensity of nausea with intensity of kinesiophobia (p<0.001), intensity of photophobia with that of phonophobia (p<0.001), intensity of kinesiophobia with worsening with physical effort (p<0.001), the degree of worsening with physical effort related to worsening with mental effort (p<0,001) and with intensity of difficulties in thinking (p=0.002); finally the degree of difficulty in thinking correlated with worsening with

mental effort (p<0.001). Global attack intensity was correlated with pain intensity and worsening with mental effort (graphic 1).

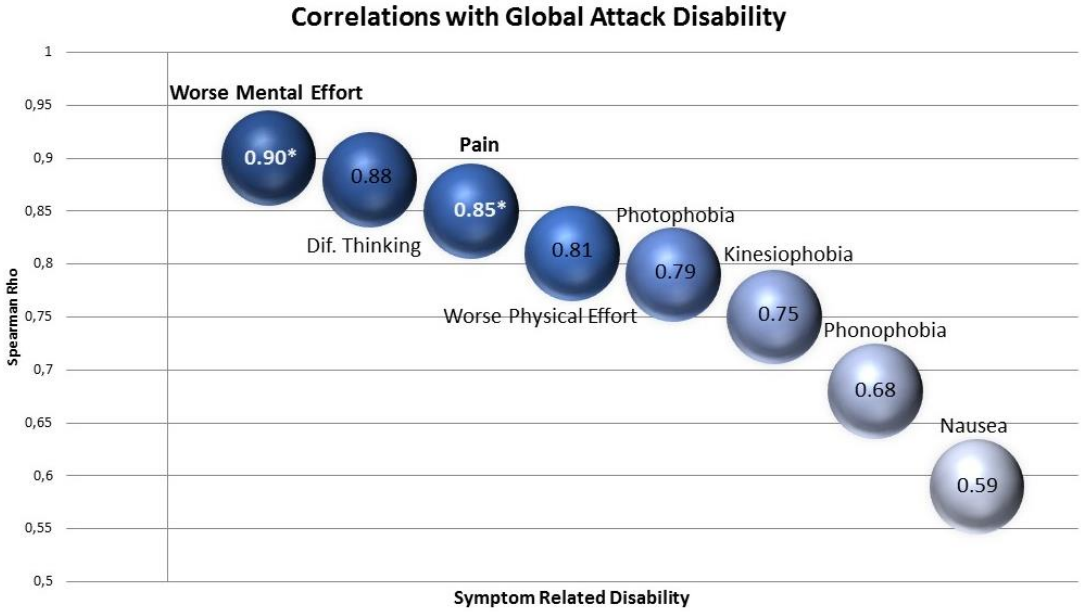
Graphic 1 – Correlation of each symptom's intensity with Global Attack Intensity



Legend: Values within balls represent Correlation Coefficients; (*) Significant correlations p< 0.001

Correlations between disability scoring for each migraine symptom were also analyzed; disability of pain had no significant correlation with any other symptoms. Disability due to nausea correlated with disability of kinesiophobia (p <0.0001), disability of photophobia correlated with that of phonophobia (p 0.002), phonophobia also correlated with the disability attributed to difficulty in thinking (p 0.003), disability of kinesiophobia with that of phonophobia (p <0.001). Disability of worsening with physical effort correlated with disability due to kinesiophobia (p 0.03) and disabilities of difficulty in thinking and worsening with mental effort were also correlated (p<0.001). Attack disability correlated to pain and worsening with mental effort (graphic 2).

Graphic 2 – Correlation of each symptom's related disability with Global Attack Disability



Legend: Values within balls represent Correlation Coefficients; (*) Significant correlations p< 0.001

The correlation of each symptom-related disability with symptom intensity revealed that disability of nausea correlated with intensity of nausea (p<0.001), intensity of worsening with mental effort (p 0.01) and intensity of difficulty in thinking (p 0.006). Disability of some symptoms correlated only with disability of the same symptom, such as with photophobia (p<0.001), phonophobia (p<0.001), kinesiophobia (p 0.004) and worsening with physical effort (p 0.004). Global attack disability also correlated with global attack intensity (p 0.008). Disability due to pain, worsening with mental effort and difficulty in thinking had no correlations with any of migraine symptoms' intensity.

GEE analysis using global attack disability as the dependent variable failed to show association with any of the studied variables (age, literacy, comorbidities, current medication, current migraine prophylactics, migraine diagnosis, disease duration, attack frequency and duration, HIT6 and Mig-SCog scores) with the exception of global attack related intensity. Gender was not included in analysis because all the individuals were females.

DISCUSSION

This prospective study of 229 migraine attacks revealed that patients are able to score intensity and disability of specific migraine attack-related symptoms independently. Patients' scores of each symptom's intensity were higher than the corresponding symptom-related disability scores, possibly reflecting self-perceived individual coping mechanisms during attacks although we cannot exclude a chance association. Amongst all proposed migraine symptoms, pain by itself was rated as having the highest intensity, had the highest disability during attacks and was correlated with global attack intensity and attack-related disability, which supports the current view that pain control measures (pain freedom, pain relief and sustained pain freedom) are adequate primary endpoint of drug trials for the treatment of acute migraine attacks(160).

Cognitive symptoms sought (worsening with mental effort and difficulty in thinking during attacks) were scored after pain both in intensity and attack related disability, followed by photophobia, phonophobia, worsening with physical effort, and kinesiophobia. Unexpected findings were the low scores attributed to nauseas' intensity and associated disability that we speculate to be related to the early use of an anti-emetic drug (in around 13% of treated attacks), associated with a pain-killer, although our study design did not allow us to test this hypothesis.

Attack-related disability was highly correlated to both pain and worsening with mental effort, suggesting that some aspects of cognitive dysfunction have a role in migraine disability, independently of other symptoms. However, with our study design, we were unable to estimate the proportion of the variability of the attack-related disability that is explained by cognitive symptoms.

Current guidelines include some other migraine associated symptoms, such as nausea, photophobia and phonophobia and a measure of total migraine freedom (instead of simple *pain* freedom) as secondary endpoints in acute migraine treatment trials(160). These guidelines do not include cognitive endpoints nor to other migraine related symptoms. This fact reflects not only the lack of therapeutic agents that are able to treat all migraine symptoms but also influences the perceived lack of control on symptoms other than pain – if we are not measuring, we will never know. The inclusion of impact and quality of life measures, medication needs and other unconventional

endpoints in prophylactic drug trials has allowed the evaluation of subtle benefits in difficult populations(161). The inclusion of measurements of cognitive impact or disability could help establish differences between acute medication profiles. To our knowledge, only two studies evaluated cognitive performance during an attack and after treatment (97, 162) as outcome measures.

In our study, none of the clinical variables analyzed had influence on symptom intensity or disability scoring. For most symptoms, their related disability correlated with its intensity reflecting that intensity is related to the disability or symptom impact. Disability due to pain and to cognitive symptoms (worsening with mental effort and difficulty in thinking) failed to demonstrate a relationship to each symptoms' intensity, suggesting that the symptoms themselves are not the major factor determining their related disability. Intensity of some symptoms was, however, related. Examples include kinesiophobia and worsening with physical effort, which is understandable if we acknowledge that kinesiophobia is a part of the avoidance behavior observed during migraine attacks, due to the aggravation of pain or enhancement of its throbbing character by head movement and/or psychical effort(45); nausea and kinesiophobia intensity were also correlated, which can be related to increased prevalence of motion sickness in migraine patients(163), as is supported by the fact that disability of kinesophobia and disability of nausea and worsening with physical effort were also correlated. The degree of worsening with physical effort was associated with the degree of worsening with mental effort and of difficulty in thinking, probably reflecting the patients' perception of the need to stop all activity.

Intensity of photo and phonophobia being related reflects the fact that sensitivity to light and sound are believed to be the clinical expression of impairment of sensory processing during attacks(164), which is supported by the fact that their associated disabilities are also correlated; using the same line of thought difficulty in thinking and worsening with mental effort intensities and disabilities are also related as both can be interpreted as cognitive dysfunction related phenomena(109, 118).

Interesting enough, pain intensity was associated with the degree of worsening with mental effort, which may reflect higher impact of the attack, as pain intensity has been shown to have some influence in attack related cognitive changes(109).The fact that we analyzed treated attacks is an obvious limitation of this study, as treatment

influences symptom intensity and symptom-related perceived disability. Treatments can also act as confounders, for cognitive symptoms and nausea can be side-effects of migraine acute medications(158, 165), although in some reports enhancement of cognitive function was reported after treatment (60, 166). We were able to identify some associations between some of the initial acute treatments used and cognitive symptoms, although the interpretation of this data is conflicting. The association of the use of triptans and combination analgesics to a higher intensity of cognitive symptoms might be either a consequence drug effects or of the choice of such more effective drugs in face of a higher intensity attack. Taking anti-emetics doesn't seem to correlate with cognitive symptoms impact yet this group was heterogeneous (included patients taking triptans, NSAIDs and analgesics). Our study design does not allow an accurate determination of the effect of each treatment in cognitive functioning, although this is an important topic for future research.

Our patient sample was clinic-based, reflecting episodic migraine patients with some comorbidities and a moderate to high impact disease (high HIT-6 score), some (38%) requiring migraine prophylactic medication. Migraine prophylactics and other chronic medications can influence cognitive performance and subjective symptom reporting(145). The co-morbidities and concomitant treatments of our study population were scarce and mild and we assumed they had little influence on cognitive or other migraine related symptoms, as reflected in GEE analysis. Although the sample was clinic-based, it does not represent the usual population of tertiary headache centers (high frequency attacks, high need for prophylactics, medication overuse and frequent co-morbidities) nor does it apply to the population-based low impact migraineur, which are limitations to the generalization of our findings. On the other hand, it was useful to select the migraine patients in whom disability is almost exclusively related to the attacks, (i.e., having low interictal impact) and having a high probability of being active and employed, strengthening the view that episodic attack-related cognitive dysfunction contributes to disability. The possibility of a recall bias is also a limitation that we minimized by having the patients to report as soon as possible (on average 14 hours) after each migraine.

The most important limitation of this study is the high attrition, as only 35% of the patients returned their diaries. Participating patients were similar to non-participating patients in all clinical variables, including disease impact and Mig-SCog

scores. There were 14% of dropouts and other potential reasons for the high attrition include the lack of financial compensation for the participants and the demography of the sample that consisted of young working adults with a moderate impact long standing disease, which failed to return to the follow-up appointment within the estimated time frame.

The benefits of treating the attacks early (first 2 hours, when the pain is mild(167)) are common knowledge for sufferers and have been documented in clinical trials and cost-effectiveness studies(168), leading to better medical counseling specially in headache clinics such as ours. An interesting observation of this study was that our population, despite having a high impact migraine and being treated and coached in a headache clinic, still waited on average 3 hours before taking their acute medication after the onset of the attack. There may be many reasons explaining this delay such as fear of side-effects, availability of medication or cost(167), yet another speculative contributing factor could relate to cognitive dysfunction, such as lack of initiative or mental slowing, to explain this delay.

There is some evidence that reversible cognitive dysfunction occurs during migraine attacks(108, 169) corroborating patients' spontaneous and subjective complaints(22, 118). Migraine subtypes and disease severity may influence the expression of such symptoms(169). The mechanisms explaining these symptoms are still elusive yet functional imaging has contributed to document changes in the human cingulated and pre-frontal cortex(153) during migraine attacks, as well as in the insula and temporal lobe(152). Interictal functional connectivity changes on executive resting state and salience networks have been documented(170, 171), as well as cortical grey matter differences of migrainous brains (172-174) . One aspect of cognitive dysfunction during attacks (worsening with mental effort) was found to correlate with attack-related disability, supplanting disability caused by nausea, photo and phonophobia, which is a reflex of its importance to migraine sufferers.

In conclusion, cognitive symptoms are important contributors to migraine attack-related disability. The cutting edge of new acute migraine drugs should evaluate the return to normal function as a primary end-point, including cognitive-related measures to evaluate the efficacy of such drugs in the return to normal cognitive performance, instead of simple freedom of pain.

A subjective cognitive impairment scale for migraine attacks - the MIG-SCOG: development and validation.

Gil-Gouveia R, Oliveira AG, Martins IP.

A subjective cognitive impairment scale for migraine attacks – the MIG-SCOG: development and validation. Cephalalgia 2011; 31(9):984-91. Impact Factor: 4.12

ABSTRACT

Background: The burden of migraine is determined by impairment during attacks, due to pain or non-painful symptoms, such as cognitive symptoms.

Objective: Development of a questionnaire to measure self-reported subjective cognitive symptoms during migraine attacks.

Methods: Item generation was accomplished through structured patient interviews analyzed by a panel of experts. A set of 43 candidate items was applied to consecutive migraine patients. Test construction with factor analysis retained 9 items. Internal consistency was assessed with Cronbach's alpha and Spearman's rho, and convergent and construct validity by correlation to spontaneous cognitive complaints, the 43-item and the Cognitive Failures Questionnaires.

Results: The 9-item Mig-SCog covers two domains, executive functions and language. Cronbachs' alpha was 0.82. It correlates with spontaneous cognitive complaints($p<0.001$), the 43-item(rho=0.69) and the Cognitive Failures Questionnaires(rho=0.61). Test-retest reliability(Cohen's kappa) was 0.55.

Conclusions: Mig-SCog is a valid, reliable, consistent working instrument of fast self-administration that quantifies subjective cognitive symptoms during migraine attacks. .

INTRODUCTION

Migraine is a highly prevalent disorder (16, 175, 176) and causes disability affecting millions of patents daily. Its overwhelming impact in world health was recognized by the World Health Organization in its 2001 *World Health Report* (177), as migraine was listed in the top 20 causes of Years of Life Lived with Disability (YLDs) worldwide, in both genders and all ages, being be responsible for 1.4% of the total of YLDs (177-179).

The disability imposed by migraine affects mostly young and active individuals, producing a significant public health and economic impact (135). Direct costs include health services and medication (135, 180) yet indirect costs represent 70% of the economic burden and result from reduced productivity at work/ school or to absenteeism (135, 137, 181, 182). The family and leisure time is also affected, with impact on both to the patient and their personal relations (135). Adding to a documented decrease in quality of life both during and between attacks, additional unaccounted indirect costs also exist, due either to inability to participate or to phobic avoidance of leisure and social activities(131, 135).

Migraines' degree of disability during attacks is determined by the frequency, duration and intensity of pain (131-136), but also from associated symptoms such as nausea and vomiting (133, 136-138). In addition, many patients report disabling cognitive symptoms (95, 133, 136, 156) and patient testing during attacks has revealed impairment in several cognitive domains such as processing speed, sustained attention/concentration, working memory, visual-spatial processing, alertness/fatigue(96, 102, 159), immediate and sustained attention and verbal learning(100).

Some authors also documented interictal mild executive dysfunction in a subgroup of migraine patients which was interpreted as a possible cumulative effect of repeated attacks(59). Further literature revealed conflicting results, showing no differences between migraineurs and controls in interictal cognitive function (183-185).

Patients often report that effective medication can relieve their pain and/or nausea but cognitive symptoms tends to persist (158), often through to the following day. Persisting symptoms are described by 80% of migraineurs and include mental tiredness,

asthenia, somnolence, depressed mood and concentration difficulties (25, 51). Acute migraine treatment with sumatriptan has been able to revert both pain and cognitive impairment in small uncontrolled trials(96, 102).

The cause of cognitive symptoms and impairment during attacks remains elusive, yet patients often complain that this type of symptoms can be as disabling as migraine pain itself. No measurement of this kind of subjective complaints exists(131-133).

Our aim was to develop a specific instrument to quantify subjective cognitive symptoms during migraine attacks. Such an instrument could contribute to the assessment of attack related disability and to monitor the effect of acute medication.

SUBJECTS and METHODS

Patients were recruited from Headache and Neurology Outpatient Clinics of two general hospitals in Lisbon, Portugal. Consecutive patients, either first or follow-up visits, who fulfilled the inclusion criteria, were invited to participate. The study protocol was approved by the Hospitals' Institutional Review Boards.

Inclusion criteria were: a) age over 16 years; b) at least second grade education (able to read and write); c) history of episodic migraine with or without aura, as defined by the ICDH-II(186); d) migraine that had be present for at least one year with a minimum of two attacks in the 3 months preceding inclusion; e) written informed consent. Exclusion criteria were chronic migraine, chronic daily headache with or without medication overuse, other headache diagnosis besides migraine, history of past or current alcohol or drug dependence or abuse, and severe or uncontrolled medical or psychiatric disorder.

Generation of scale items

Structured interviews with consecutive migraine patients (n=37) from the outpatient headache clinic were conducted in order to identify cognitive symptoms during migraine attacks. From this patient-centered data, an expert panel of three neurologists with experience in headache and cognition selected relevant items and generated new items based both on cognitive complaints commonly described by patients during migraine attacks and on a relevant medical literature review. The panel also evaluated wording

for complexity and ambiguousness and supported item relevance and validity(187). This process resulted in a draft questionnaire that included an initial open-ended question – "Do you feel your mental capacities are different during your headache attacks? Please describe your main difficulties." - followed by 43 multiple choice questions, asking about several domains of cognitive function during the attacks. Applicability and understandability of questions was evaluated by a focus group of 10 migraine patients.

Patients had to self-rate each item-symptom in a 3 option scale - occurring often (scoring 2 points), rarely (scoring 1 point) or not at all (scoring 0) during the attacks; it was also possible to answer "don't know, don't want to answer", to access item comprehensiveness and adequacy. Some questions with reversed or clearly unrelated responses were included in order to access the no/ yes-saying bias(187).

The draft 44-item self-administered questionnaire was applied to 93 consecutive migraine patients interictally, immediately after their routine clinical appointment. Demographic and clinical data was collected and analyzed (age, gender, literacy, migraine diagnosis and characterization, disease duration, prophylactic medication use (yes/no)). One of the authors checked the forms for completeness.

For item reduction, items that performed poorly because of a high level (>10%) of "don't know, don't want to answer" responses were eliminated from the start. Factor analysis with varimax rotation of the remaining items was used to identify likely domains of cognitive function. Items with an eigen value of 0.400 or higher were retained unless they had an eigen value difference inferior to 0.300 between any two factors. The result was a simplified 9-item multiple choice self-administered questionnaire – the Mig-SCog – with a total score varying from 0 to 18, the highest scores representing more expressive cognitive symptomatology during attacks.

Statistical Analyses

Construct validity of the Mig-SCog was assessed by analyzing the spontaneous symptoms evoked by the first open question in number and content, and by using this as an empirical measure to infer the meaning of the total questionnaire score. The average number of spontaneous cognitive symptoms reported during the attacks was correlated with demographic and clinical variables (age, gender, literacy, disease duration, type of

migraine, average intensity, frequency and duration of attacks, current use of prophylactic medication) and with total score of the 43-multiple choice questionnaire. Qualitative analysis was performed by an expert panel of neurologists with experience in cognitive testing, who categorized the symptoms reported in non-cognitive and cognitive domains in both the spontaneous cognitive complaints and the questionnaires.

Internal consistency was assessed with Cronbach's alpha and the lower bound of the one-sided 95% confidence interval. Inter-item, item-test and item-rest correlations were tested with Spearman's rank correlation (□) and Cronbach's alpha. The item was included in the total score for item-test correlations, but the item was excluded in the item-rest correlations and Cronbach's alpha. The same methods were used to analyze dimensions within the final instrument: interdimension, dimension-total and dimension-to-own correlations and Cronbach's alpha.

In order to provide evidence of external validity, convergent validity was assessed by correlating the reduced Mig-SCog scores to scores of the Cognitive Failures Questionnaire(188) – applied to 31 patients selected at random. This is a self-rated questionnaire that measures frequency of memory and cognitive failure behaviors in daily life, spanning the most frequent cognitive symptoms and domains(188). To assess test-retest reliability, the simplified 9-item self-administered questionnaire was applied within a 3 month interval to a random sample of 33 patients. The agreement for each item was tested by Cohen's kappa and the correlation between total scores was tested with Spearman's correlation coefficient. The simplified 9-item Mig-SCog was applied to a subsample of patients (n=33) who also rated themselves interictally, that is, referring to when they are not having an attack. Average scores were compared using the paired t-test.

Associations between patient variables and Mig-SCog socres were investigated with the Pearson's correlation coefficient (continuous variables) or t-tests (binary variables). Using Ronald Fisher's classic z-transformation to normalize the distribution of Pearson's correlation coefficient (189), the sample size of this study has at least 80% power, with a 5% type-I error, to indentify an association between Mig-SCog scores and patient variables having a true correlation coefficient of 0.30 or more.

Statistical analysis was done with SPSS v16.5 (Statistical Product and Service Solutions, Chicago, IL) and STATA 11 (Stata Corporation, College Station, TX)

RESULTS

The preliminary study group consisted of 37 patients (28 females), of whom 12 had migraine with aura. The group had an age average of 36.4 years, mean disease duration of 16 years and an average MIDAS score of 16.4 on the previous 3 months. The majority of patients had 1-4 attacks monthly (67.6%), the attacks lasted less than 24h in 51.4% and were of moderate to severe intensity in 64.9%.On average, each patient described four frequent and 3.5 infrequent cognitive symptoms during migraine attacks. These data were used to select the initial candidate items for the self-administered questionnaire.

The main study group consisted of 93 patients (86 females), 18 having migraine with aura. Age average was 39.2± 11.6 years (range 18 to 83 years), average years in school were 11.7 ± 5 years (range 2 to 22 years) and mean disease duration was 18.4± 11.2 years (range 1 to 57 years). The majority of patients (53.8%) had 1-4 attacks monthly, most attacks lasting 4 to 24h (53.8%) and usually of moderate to severe intensity (98.9%). Sixty seven patients (72%) were currently doing migraine prophylactics.

Answers to the first open question generated on average 3.3 ± 1.6 cognitive symptoms by patient, ranging from 0 to 9. The number of cognitive symptoms reported was not shown to be associated with any of the patient variables studied.

Qualitative analysis of cognitive symptoms allowed its grouping in 21 items. These items were then analyzed and classified into cognitive and non cognitive symptoms. We observed that 37% of spontaneous complaints were not purely cognitive yet all were related to known attack-related symptoms that are recognized as able to interfere with global function during attacks. Non cognitive symptoms included humor/ anxiety changes (feelings of impatience, irritability, intolerance, sadness, despair, panic, lack of self-control, n= 47), specific symptoms related to avoidance behaviors during the attacks (visual, noise, movement and physical effort intolerance, n= 44) and eviction itself (need for isolation and to stay still, eviction of social contact, n=10) and global feelings of tiredness, exhaustion, dizziness, lack of balance or even changes in appearance (n=13).

The most common reported symptoms were specific of cognitive domains (63%) and included attention (difficulty in thinking, decreased attention or concentration, mental confusion, trouble in studying, difficulty in performing mental calculation (n=84), planning (difficulties in routine chores such as cooking, domestic chores, working,

driving, in doing two tasks at a time, in resolving or organizing the day, n=29), lack of initiative (feeling impaired, “anesthetized”, diminished or blocked, “dumb”, decreased initiative, unable to take action, react or to decide, having trouble doing everything, n=25), language (difficulty in speaking, talking, understanding when being spoken to, writing, forgetting peoples and objects names, n=24), processing velocity (slowness of thinking, slowness when moving, needs more effort to do basic things, everything takes more time, more time to learn new information, n=20) and memory (lack of memory, empty mind, forgetfulness, forgetting to take pain killers, n=12). None of the patient variables was related neither to the number of spontaneous cognitive symptoms nor to the score of the 43-item questionnaire (p ns). Factor analysis with varimax rotation retained 4 factors explaining 70.6% of the observed variance and allowed item reduction to a 9-item questionnaire (tables 1&2).

Table 1 - The Mig-SCog questionnaire (English Translation)

During your Headaches, do you…

…feel confused?	☐ Often	☐ Sometimes	☐ No
…have trouble performing tasks at your normal speed?	☐ Often	☐ Sometimes	☐ No
…have trouble following a route (driving or walking)?	☐ Often	☐ Sometimes	☐ No
…have trouble thinking?	☐ Often	☐ Sometimes	☐ No
…have trouble maintaining the tread of your thoughts?	☐ Often	☐ Sometimes	☐ No
…have trouble in understanding when being spoke to?	☐ Often	☐ Sometimes	☐ No
…have difficulty in organizing a sentence or a conversation?	☐ Often	☐ Sometimes	☐ No
…have trouble speaking out other people’s names?	☐ Often	☐ Sometimes	☐ No
…have trouble in remembering the correct objects names?	☐ Often	☐ Sometimes	☐ No

The reduced 9-item Mig-SCog had a completion time of around 1 minute. The average score was 8.63 ± 4.04, ranging from 0 to 18 (graphic 1). The score of the reduced 9-item the Mig-SCog was not influenced by gender (p=0.16), presence of aura symptoms (p=0.54), current migraine prophylaxis (p=0.43), age (p=0.63), disease duration (p=0.78), attack frequency (p=0.10), duration (p=0.44) and intensity (p=0.98), but was

associated with the total number of spontaneous cognitive complaints (p < 0.0001) and to lower literacy (p= 0.009).

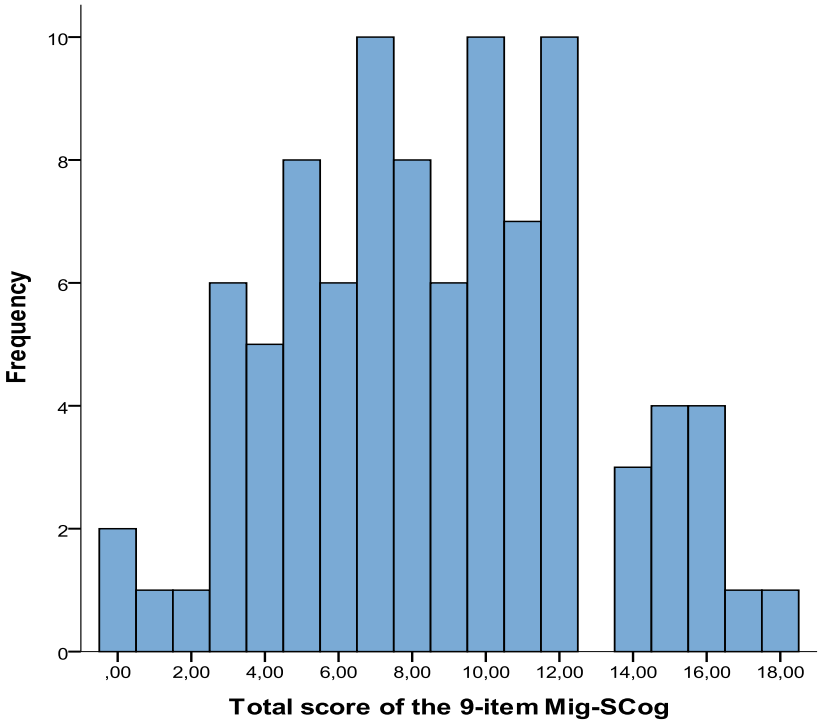
Table 2 – Four Factors of the Mig-SCog

	Explained Variance	Chronbach Alpha
Factor 1 – Attention/ processing speed/ orientation		
… do you feel confused? … do you have trouble performing tasks at your normal speed? … do you have trouble following a route (by driving or walking)?	22,2%	0.74
Factor 2 – Language		
… do you have trouble in understanding when being spoke to? … do you have difficulties in organizing a sentence or a conversation?	17,4%	0.70
Factor 3 – Language – Naming		
… do you have trouble speaking out other people's names? … do you have trouble in remembering the correct objects names?	15,7%	0.79
Factor 4 – Planning/ attention		
… do you have trouble maintaining the tread of your thoughts? … do you have trouble thinking?	15,4%	0.74

The reduced 9-item Mig-SCog had a completion time of around 1 minute. The average score was 8.63 ± 4.04, ranging from 0 to 18 (graphic 1). The score of the reduced 9-item the Mig-SCog was not influenced by gender (p=0.16), presence of aura symptoms (p=0.54), current migraine prophylaxis (p=0.43), age (p=0.63), disease duration (p=0.78), attack frequency (p=0.10), duration (p=0.44) and intensity (p=0.98), but was associated with the total number of spontaneous cognitive complaints (p < 0.0001) and to lower literacy (p= 0.009).

Cronbach's alpha of the reduced Mig-SCog was 0.82 (lower bound of the one-sided 95% confidence interval ≥ 0.77). The median inter-item correlation coefficient was 0.34 (range 0.05 to 0.56), the median item-test ρ was 0.68 (range 0.46 to 0.73) and the median item-rest was 0.56 (range 0.33 to 0.62). The median item-rest Cronbach's alpha was 0.80 (range 0.79 to 0.82).

Graphic 1 - Total score of the reduced 9-item Mig-SCog questionnaire



The median interdimension ρ was 0.49 (range 0.36 to 0.60). Dimension-total Cronbach's alpha was 0.79 and correlation coefficients ranged from 0.71 to 0.84. The dimension-to-own alpha ranged from 0.70 to 0.79, and the correlation coefficients ranged from 0.50 to 0.70.

Construct validity of the reduced Mig-SCog scores was confirmed by the high correlations to the 43-item draft questionnaire scoring (Spearman's ρ 0.69, $p<0.001$) and to the total score of the Cognitive Failures Questionnaire (188) (Spearman's ρ 0.61, $p<0.01$).

Test-retest reliability of the 9-item the Mig-SCog revealed a highly significant ($p<0.0001$) Cohen's kappa for each item, ranging from 0.58 to 0.76 (respectively 0.58 for items 1, 2 and 5, 0.62 for item 9, 0.66 for item 8, 0.71 for item 7, 0.74 for items 4 and 6 and 0.76 for item 3). Cohen's kappa for the 9-item Mig-SCog was 0.55 ($p= 0.001$) and Cronbach's alpha ranged from 0.84 to 0.88, from first to second application of the questionnaire. Correlation of total scores in both applications was high (Spearman's ρ 0.91, $p <0.01$)

A significant difference was shown between ictal versus interictal scores in the subsample of 33 patients (8.0 ± 4.3 *versus* 1.5 ± 2.7, respectively, $p<0.0001$).

DISCUSSION

Cognitive symptoms occur during migraine attacks and are often not reversed by effective pain treatment(158) nor contemplated as a valid end-point in acute treatment migraine trials (190). Cognitive symptoms during attacks contribute substantially to reduced ability to carry out activities(95) and therefore to migraine burden, yet no instrument exists to identify and quantify this type of symptoms.

The use of detailed neuropsychological testing during migraine attacks is not practical and currently available generalist testing instruments (191) are long, unspecific and unpractical for everyday clinical practice. Available subjective scales for cognitive symptoms are very often related to progressive neurological disorders and are developed to predict cognitive decline(192-196).

We aimed to develop an instrument that would be patient-centered and disease-related. It also should be self-administered, of fast application, easily understandable, requiring a minimal literacy and cross-cultural. Although subjective, it should allow quantification and be versatile, being used either in relation to the usual headache pattern or to a specific migraine attack.

As no instrument as such existed previously, the main methodological difficulty of this study was item generation and selection. Item generation was clinical-based, relying on patients' self-report of cognitive symptoms during migraine attacks, identified by open-ended questions in a structured interview. Items generated were complemented by a panel of headache experts after relevant literature review (197). An extensive item list was then produced, to ensure that infrequent yet possibly relevant symptoms were contemplated. After analysis for language adequacy and item comprehension by a focus group, the extensive questionnaire was applied, yet still including an initial open-ended question, to ensure no relevant cognitive domain had been missed and to access construct validity. This effort to be as comprehensive as possible had the objective of not missing potentially relevant items to migraine. No effort was made to include cognitive symptoms that were infrequent in migraine nor to have the same representativity of each domain by defining the number of items allowed in each domain. It was expected that only a few cognitive domains would prevail, if the questionnaire was to be universally accepted by migraine patients. As it is a patient-based questionnaire, the domains identified were expected to most probably represent the main practical

cognitive difficulties present in everyday life chores and not necessarily the cognitive functions that were demonstrated to be impaired in cognitive testing during attacks (96, 100, 102, 159).

Item reduction was first accessed by the ability of items to generate responses: Items with non-response rates of 10% or higher were eliminated. Exploratory factor analysis was used to identify conflicting or confounding items that could be attributed to several cognitive domains - these were systematically eliminated. The purpose was to obtain a clear and short questionnaire that would perform adequately on internal consistency, concurrent validity and test-retest reliability. As the process went along, qualitative analysis of the spontaneous cognitive symptoms reinforced its construct validity.

The final 9-item Mig-SCog questionnaire is simple, reliable, and internally consistent and it has good temporal stability. Its performance is in line with an existing cognitive functions questionnaire(188), a good measure of everyday cognitive difficulties for young adulthood that has good correlation with laboratory evaluation (198). Mig-SCog reflects only two cognitive domains – Executive functions (attention/ processing speed/ orientation / planning) and Language (naming and language), that are the most frequent spontaneous complaints of patients in everyday life and some the range of executive defects identified in objective testing of Migraine patients during attacks(96, 100, 102, 159). This is not the same as stating that these are the only symptoms expected to occur during migraine attacks, but that these are the most probable to be consistently reported by patients and, therefore, to be representative of their most troublesome cognitive symptoms. The Mig-SCog rating is significantly higher when patients refer to attacks compared to the interictal period, suggesting that cognitive symptoms during attacks are beyond everyday cognitive difficulties. As an example, low processing speed and difficulties in planning may explain a common clinical observation that patients within a migraine attack are often unable to get around to take their acute medication, a fact that has important implications in efficacy of pain relief and attack impact (199, 200).

Our results show that the Mig-SCog questionnaire is a new working instrument that is versatile and may be applicable, in the future, both in clinical practice and in research settings, without significantly increasing patient evaluation time. Its scoring was only influenced by literacy, despite literacy had no influence on the number of spontaneous cognitive symptoms reported. This suggests that less literate individuals tend to overrate

the frequency of cognitive symptoms during attacks, probably because of a baseline lower cognitive performance(201, 202).

The Mig-SCog score was independent of any other clinical variable, leading to speculation that the expression of cognitive symptoms is attack-related and not disease-related, much like the clinical expression of all other symptoms of a migraine attack.

It is recognized by the authors that more work needs to be done on validation of this instrument to other languages, such as English, and also to study its performance in cohorts of patients in different clinical settings and in other headache types. Limitations of this study are acknowledged, namely the possible effect of the recall bias, as the date of the last attack was not sought out. However, since neither the frequency nor the intensity of attacks was related to higher scoring on the Mig-SCog we think this bias is unlikely to be present. Another limitation is the absence of data regarding the type of migraine preventives used in this sample, as well as other relevant psychoactive drugs that could influence the occurrence of cognitive symptoms. The use of preventives was not related to any specific complaint nor scale item or total score of the Mig-SCog.

Sometimes the obvious needs to be stated (1) migraine acute therapy is not only about pain control. The ideal migraine drug must also contemplate non-pain related symptoms that contribute significantly to disability, so instruments that identify and quantify these symptoms are essential to improve migraine treatment strategies; (2) migraine related cognitive symptoms during attacks are real and disabling. Researchers need an instrument to evaluate the contribution of cognitive symptoms to impairment during attacks and physicians need a fast quantifiable report of cognitive symptoms by their patients, to redefine treatment strategies. Mig-SCog also offers patients an easy and quantifiable way of measuring ill-characterized, difficult to express, disabling symptoms to their attending physicians.

The Mig-SCog could be the first practical contribution to allow the valorization of cognitive symptoms of migraine patients during attacks. Hopefully, the importance and impact of these symptoms will be recognized in future guidelines of migraine trials, either as a valid endpoint of acute treatment efficacy (190) or as a part of the assessment of migraine's impact.

Clinical Utility of the Mig-SCog

Gil-Gouveia R, Oliveira AG, Martins IP. *Clinical Utility of the Mig-SCog*.
[submitted]

ABSTRACT

Background: Mig-SCog is a tool developed to quantify subjective cognitive complaints during migraine attacks. Yet, cognitive symptoms are frequent in everyday life, in non-headache pain and in non-migraine headache.

Objective: To evaluate the Mig-SCog specificity for migraine-related cognitive impairment and the reliability of Mig-SCog scores obtained outside attacks.

Methods: Mig-SCog scores were compared a) between migraine and tension-type headache (TTH) patients; b) in migraine patients between migraine attacks, non-headache pain and pain-free status; c) in migraine patients during and outside a migraine attack.

Results: Two-hundred and forty eight patients (51 TTH) were included; Migraine patients scored their attacks higher than TTH in the total Mig-SCog (8.0±4.1 *versus* 3.4±3.2, $p<0.0001$), with differences found in all scale items ($p<0.0001$) except those related to naming (8 and 9). The AUC of Mig-SCog score for the diagnosis of Migraine was 0.835 (95% CI of 0.763-0.906, $p< 0.0001$). Migraine patients rated the Mig-SCog higher for migraine (7.9±4.6) than for non-headache pain (2.3±2.9, $p<0.0006$) or pain free (1.6±2.4, $p<0.0006$). Scores regarding migraine attacks obtained during and outside an attack were similar (7.4±4.4 *versus* 6.9±4.0).

Conclusions: Attack-related subjective cognitive symptoms, evaluated with the Mig-SCog, differ between migraine and TTH patients, particularly in items related to executive functions (processing speed and attention) and language (sentence production and understanding). The Mig-SCog applied to migraine patients produces higher scores related to migraine than to non-headache pain or being pain free; patient scoring by memory for usual attacks is equivalent to scoring within attacks, demonstrating negligible recall bias.

INTRODUCTION

The Mig-SCog(118) is a brief subjective assessment tool developed to identify and quantify subjective cognitive symptoms of migraine attacks. Attack-related cognitive dysfunction has been documented in executive, memory and language functions in most of the studies addressing reversible neuropsychological impairment during attacks (60, 96, 98, 100, 102, 109, 159, 203). These symptoms contribute to attack-related disability and may not be relieved by acute migraine medication (95, 158). In addition, cognitive dysfunction occurs as a side effect of some prophylactic migraine drugs(204), which may increase attack-related difficulties.

The Mig-SCog was developed based on subjective cognitive complaints of migraine patients, and is a self-administered nine-item questionnaire (118). The instrument is directed to the main difficulties reported by patients during migraine attacks and has good psychometric properties (internal consistency reliability and test-retest reliability) as demonstrated in a previous study(118). As it is fast and easy to apply, requiring only paper and pen, it is therefore a simple and inexpensive clinical instrument.

The use of this instrument in daily clinical practice may help patient-doctor communication in the assessment of these symptoms. Particularly interesting aspects relate to treatment effectiveness or to restoring of normal function after an attack(95). Work productivity is perceived to be around 54% impaired during a migraine attack(92) and part of this self-perceived impairment could be related to cognitive dysfunction. However, cognitive symptoms are quite common, even in the younger population, and are generally associated with stress or sleeping disorders (142, 205). Therefore, an important property of this tool would be its ability to distinguish common cognitive symptoms that had been aggravated by a superimposed migraine attack, from migraine-related subjective cognitive symptoms.

The aim of this study was to further evaluate the Mig-SCog regarding aspects that relate directly to the usefulness of its clinical application. Specifically, we wanted to get answers to three questions: 1) does the Mig-SCog score cognitive symptoms differently in migraine patients and in tension-type headache patients?; 2) do migraine patients

score the Mig-SCog differently between migraine attacks, pain-free periods and non-headache pain situations? 3) does the Mig-SCog measure migraine-related cognitive difficulties only when administered during an attack, or is it reliable to score it during pain-free periods?

In order to answer these questions, we designed a study comprising the following evaluations: 1) comparison of Mig-SCog scores between patients with migraine and with tension-type headache; 2) comparison of Mig-SCog scores when migraine patients referred to three different situations - a typical migraine attack, a non-headache painful situation (e.g. menstrual or low back pain) and a pain-free period.); 3) comparison of Mig-SCog scores, in a different sample of migraine patients, when scoring occurred during an actual migraine attack and when scoring was done outside an attack.

SUBJECTS and METHODS

Population

Participants were recruited consecutively on a Headache Outpatient Clinic, both from first or from follow-up visits, and invited to participate. Inclusion criteria were: a) age between 16 and 65 years; b) minimum of four years of education ; c) minimum headache frequency of one monthly attack in the 3 months preceding inclusion; d) written informed consent of adult patients or their legal guardians in the case of patients aged 16 and 17; e) having a single headache diagnosis, either definite episodic migraine with or without aura or episodic or chronic tension-type headache, according to ICDH-III(186); f) for the part of the study comparing Mig-SCog' scores during with in-between migraine attacks, living or working within or nearby the study center was required (to improve accessibility).

Exclusion criteria were the simultaneous presence of migraine (either with or without aura) and tension-type headache, or the additional presence of any other headache type, including chronic migraine with or without medication overuse as well as the presence of systemic or psychiatric diseases with potential influence of cognition. History of substance abuse and current medications with potential influence on cognition other than migraine prophylactics was also an exclusion criteria. The study protocol was approved by the Hospital's Institutional Review Board.

Study design

Recruitment and inclusion were carried out by a headache specialist (R.G.G.) at a regular clinic visit, who verified the study eligibility criteria and carried out a standard clinical evaluation. Patients were asked to complete the Mig-SCog(118) at the end of the appointment and to return it immediately to the doctor or the secretary. Data collected from the Mig-SCog included answers to nine items, presented as graded scores (0: absence of the symptom; 1: the symptom occurring sometimes during headache attacks; 2: the symptom occurring often during headache attacks. The items relate to two cognitive domains: executive function (items 1, 2 and 3 directed to symptoms of decreased attention, processing speed and orientation, and items 4 and 5 relating to planning and attention) and language (items 6 and 7 relating to comprehension and speech production, and items 8 and 9 to naming abilities). Total Mig-SCog score is computed by adding up the scores of the nine scale items.

According to the diagnosis and headache status, patients were asked to participate in one of three evaluations:

1 - Discrimination of cognitive difficulty between migraine and tension-type headache: This part of the study included patients with a history of migraine and patients with a history of tension-type headache, using the ICDH-III(13) diagnosis as the gold standard.

2. Discrimination of cognitive difficulties during migraine attacks from non-headache pain and from pain-free periods: This part of the study included migraine patients, who were asked to complete three Mig-SCog scales, each one with a different header: “During your headaches…”, “During a non-headache pain (such as low-back pain or menstrual pain)….” and “When you are pain free…“. . Therefore, patients would score the instrument by referring to their baseline pain-free status, to their usual migraine attacks and to a non-headache pain.

3. Comparing the Mig-SCog scored during and outside an attack: This part of the study included migraine patients that were asked to score the Mig-SCog twice, once during a migraine attack and other in a headache free period. The Mig-SCog headers differed in the two situations: when applied during the attack it read “In this moment…” and when applied in the headache-free status it read instead of “During your headaches…”

Additional attack information was also collected, such as current pain intensity and duration of headache since its onset. Some patients were recruited on a headache day, in an emergency visit at the clinic, while others were recruited on a headache free day, and these were asked to return specifically on a headache day. In both groups, if acute treatment had been used in the 8 hours previous to the evaluation, the patient was excluded. Interval between evaluations could not be less than one month in order to minimize the learning effect.

Statistical Analyses

Descriptive statistics are presented as absolute and frequencies or mean ± standard deviation. Patient characteristics were compared between groups with Student's t-tests and chi-square tests as appropriate.

In the study comparing migraine and TTH patients a ROC curve was plotted and the area under the curve (AUC), or *c*-statistic, determined. Each item of the Mig-SCog was recoded as binary variable (0 indicating absence of the symptom and 1 indicating presence of the symptom, whatever its frequency during the attacks) so that the sensitivity, specificity, positive and negative predictive values and likelihood ratio of each questionnaire item could be computed.

In study comparing migraine patients' Mig-SCog scores referred to three different situations, the normality of the Mig-SCog scores was tested using the Shapiro-Wilk test. As normality could not be assumed, the non-parametric Friedman test was used to compare total Mig-SCog scores and individual item scores between the three different situations within each subject. Differences between migraine and the two other situations were tested with the sign test, adjusting *p*-values for multiplicity using the Bonferroni correction(206).

In the study where migraine patients were asked to score the Mig-SCog outside and within an attack, scores were compared using the sign test. To evaluate test reliability the Intraclass Correlation Coefficient was calculated for the total score and for each item. Statistical analyses used SPSS v20. All statistical tests are two-sided and significance level was set a $p<0.05$.

RESULTS

1– Discrimination of Migraine and Tension-type headache

One patient was excluded for not completing all of the Mig-SCog. The total study population of this part of the study consisted of 149 subjects: 98 with migraine (13 with aura) and 51 with tension-type headache (23 frequent episodic, 28 chronic). There were 126 females (84.6%), eight left-handed, the average age was 32.6 ± 8.7 years (range 18 to 65 years) and the number of years of education was 14.7± 1.7 (range 9 to 20 years). Forty patients (27%) were on prophylactic headache treatment with amitriptyline (8), topiramate (18), propranolol (9), valproic acid (4) and lamotrigine (1).

The characteristics of migraine and tension-type headache patients are shown on table 1.

Table 1 – Population characteristics of the first part of the study (comparing migraine with TTH)

	Migraine	**Tension-Type Headache**	**p-value**
Sample Size (N)	98	51	---
Females	90(91.8%)	36 (70.6%)	0.001
Education (years)	15.0 ± 1.5	14.1 ± 2.0	0.005
Age at inclusion (years)	31.4 ± 7.5	34.9 ± 10.2	0.070
Disease duration (years)	15.4 ± 9.3	8.2 ± 10.0	<0.0001
Medical Comorbidities	30 (30.6%)	24 (47.1%)	0.052
Prophylactic treatments	37 (37.8%)	3 (5.9%)	<0.0001
Diagnosis - Migraine (with/without aura) - TTH (episodic/ chronic)	 85 (13.3/86.7%) ---	 --- 28 (45.1/54.9%)	---

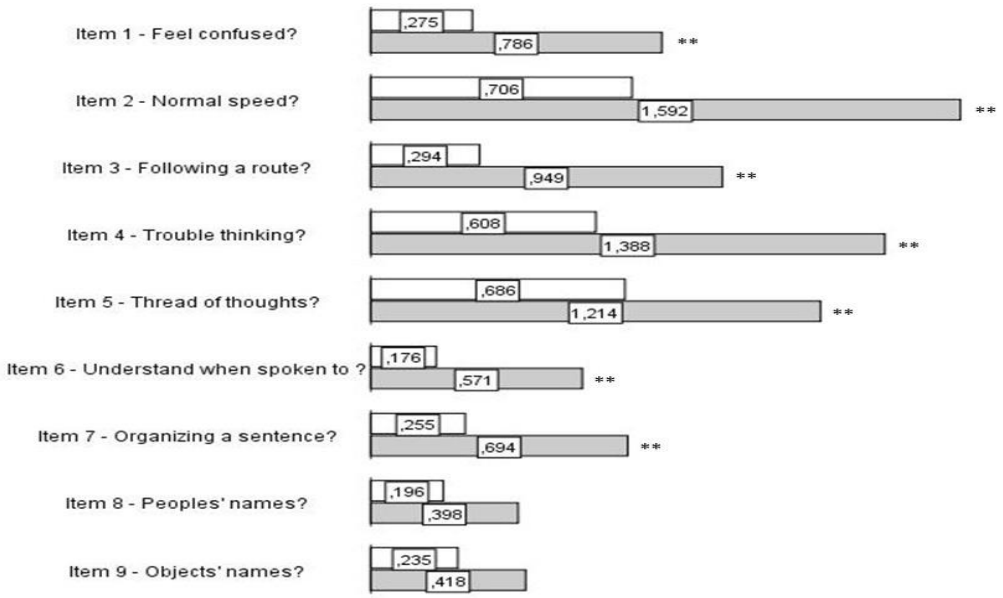
Migraine patients were more often females and their literacy was slightly higher literacy (one year, on average) than tension type headache patients; migraine patients also had longer disease duration and higher rates of prophylactic treatment. Headache characteristics were, as expected, very distinct between the two diagnoses (table 2).

Table 2 – Headache characteristics of Migraine and Tension Type Headache patients

	Migraine	Tension-Type H.	p*-value
Frequency (episodes/ month)	5.3 ± 5.0	16.7 ± 11.4	<0.0001
Attack duration (average in hours)	47.4 ± 32.2	15.6 ± 24.5	<0.0001
Intensity (Severe)	52 (53.1%)	2(3.9%)	<0.0001
Unilateral pain	54 (55.1%)	8 (15.7%)	<0.0001
Maximum pain location - Trigeminal - Posterior - Hemi/ holocrania	 80 (81.6%) 7 (7.1%) 11 (11.2%)	 27 (52.9%) 11 (21.6%) 13 (25.5%)	 0.001
Quality (Throbbing)	79 (80.6%)	1 (2.0%)	<0.0001
Associated symptoms - Nausea - Vomiting - Photophobia - Phonophobia - Kinesophobia - Worsening with physical effort - Aura	 92 (93.9%) 23 (23.5%) 95 (96.9%) 88 (89.8%) 86 (87.8%) 94 (95.9%) 15(15.3%)	 8 (15.7%) 1 (2.0%) 12 (23.5%) 22 (43.1%) 2 (3.9%) 1 (2.0%) 0 (0%)	 <0.0001 0.001 <0.0001 <0.0001 <0.0001 <0.0001 0.003

Average Mig-SCog total score in this population was 6.4 ± 4.4, ranging from 0 to 18; migraine patients had a significant higher average score (8.0 ± 4.1) than tension-type headache patients (3.4 ± 3.2, p<0.0001). Comparative analysis of mean scores in each item of the Mig-SCog is depicted in Figure 1.

Figure 1 – Comparative analysis of Mig-SCog in each diagnosis, per item (sub-study 1)



Legend: Gray bars: Migraine, White bars: Tension-type headache ; Values within bars represent Mean Item Scores;

** Difference between Tension-Type Headache and Migraine is significant p<0.0001

Differences between migraine and tension-type headache are significant (p<0.0001) in items 1 to 7 but not in items 8 and 9 (having trouble in speaking other people's names and having trouble recalling the correct name of objects). The difference in Mig-SCOg scores between migraine and TTH patients was maintained at the p<0.0001 level after adjustment with multiple regression by gender, age, literacy, disease duration, presence of other medical conditions, current medication and current prophylactic medication.

The ROC Curve for the total Mig-SCog score is depicted in Figure 2; the area under the ROC curve (AUC) is 0.835 (95% confidence interval 0.763 to 0.906, p< 0.0001). The sensitivity, specificity, positive and negative predictive values and the likelihood ratio of each of the items of the Mig-SCog is shown in table 3.

Figure 2 – ROC Curve of the Mig-SCog total score, for the diagnosis of Migraine (sub-study 1)

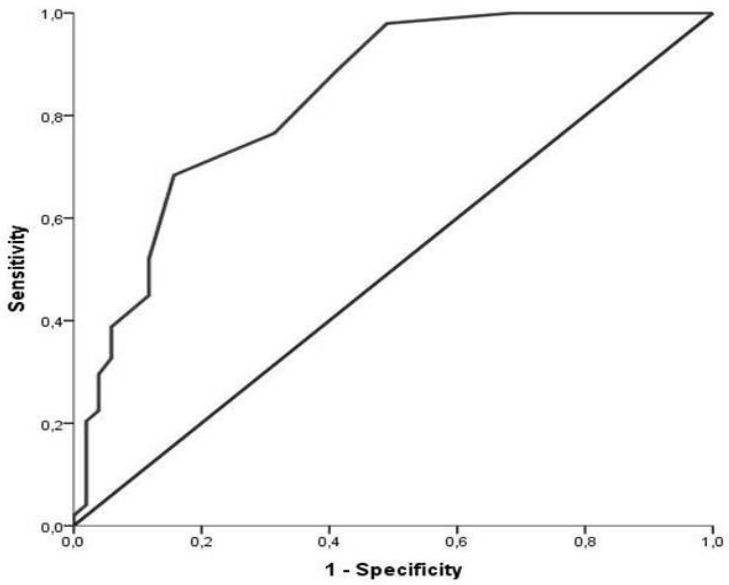


Table 3 - Performance of each item of the Mig-SCog, for the diagnosis of Migraine

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Likelihood ratio (95% CI)
Mig-SCog Items					
Item 1 (confused)	0.582 (0.575-0.732)	0.745 (0.601-0.852)	0.814 (0.700-0.894)	0.481 (0.368-0.596)	2.28 (1.39-3.76)
Item 2 (speed)	0.990 (0.936-0.999)	0.392 (0.262-0.539)	0.758 (0.673-0.827)	0.952 (0.741-0.998)	1.63 (1.30-2.03)
Item 3 (route)	0.724 (0.623-0.808)	0.706 (0.560-0.821)	0.826 (0.725-0.896)	0.571 (0.441-0.693)	2.46 (1.58-3.86)
Item4 (thinking)	0.959 (0.893-0.987)	0.451 (0.314-0.595)	0.770 (0.684-0.840)	0.852 (0.654-0.951)	1.75 (1.36-2.25)
Item 5 (thread of thoughts)	0.847 (0.757-0.909)	0.392 (0.262-0.539)	0.728 (0.635-0.805)	0.571 (0.395-0.732)	1.39 (1.10-1.76)
Item 6 (understand)	0.469 (0.369-0.572)	0.863 (0.731-0.938)	0.868 (0.740-0.941)	0.458 (0.357-0.563)	3.42 (1.66-7.02)
Item 7 (organizing sentences)	0.510 (0.408-0.612)	0.765 (0.622-0.867)	0.806 (0.682-0.892)	0.448 (0.343-0.558)	2.17 (1.27-3.69)
Item 8 (naming people)	0.296 (0.210-0.398)	0.843 (0.709-0.925)	0.784 (0.613-0.896)	0.384 (0.295-0.481)	1.89 (0.93-3.82)
Item 9 (naming objects)	0.357 (0.265-0.461)	0.804 (0.664-0.897)	0.778 (0.625-0.883)	0.394 (0.301-0.495)	1.82 (0.98-3.37)

Legend: PPV – Positive Predictive Value; NPV – Negative Predictive Value;

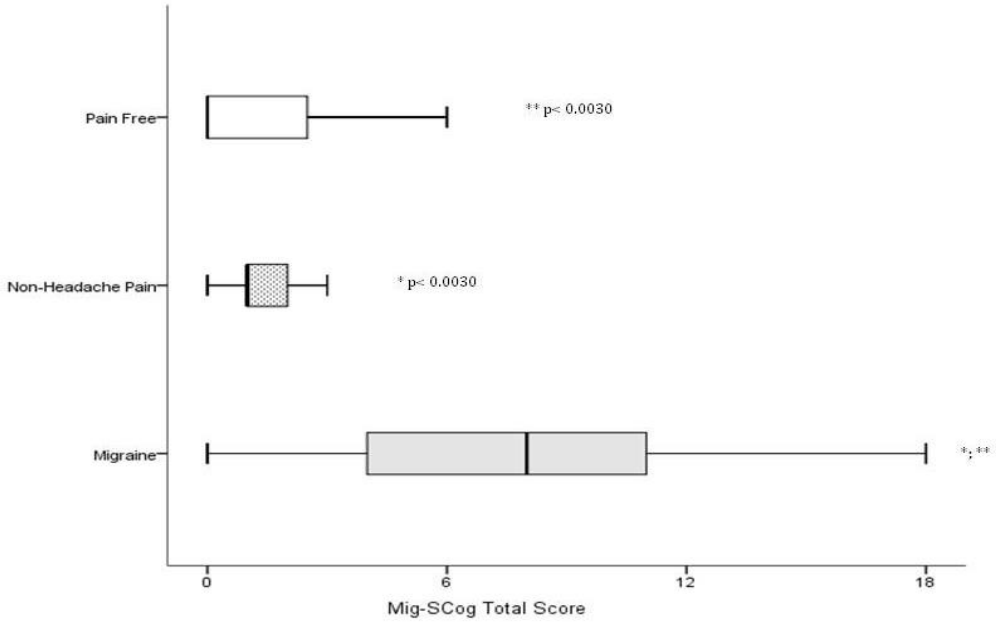
2. Comparison of Migraine with Non-Headache pain and Pain-Free

Sixty-seven patients were included in this part of the study, 4 (6 %) were excluded (1 with chronic migraine, 3 with concomitant tension-type headache). The final population of 63 migraine patients included two left-handed individuals, 8 males (12.7%) and 6 (9.5%) patients with aura. The average age was 36.9 ± 10.5 years (range 16 to 60 years) with 15.4± 4.0 years of literacy (range 6 to 23 years).

The average attack frequency was 5.5±5.4 attacks monthly, lasting on average 29.8 ± 25.8 hours, the vast majority being of moderate (73%) to severe(23.8%) intensity. Twenty-one participants (33.3%) were receiving migraine prophylactics, either propranolol (7), valproic acid (5), amitriptyline (2), topiramate (2) and 5 were taking combined prophylaxis (valproic acid with amitriptyline 2, topiramate with propranolol 2 and topiramate with amitriptyline 1). This population had an average HIT-6 score of 60.8 ± 7.2 (range 43 to 76).

The average Mig-SCog total score for migraine pain was 7.9 ± 4.6 (range 0 to 18), for non-headache pain was 2.3 ± 2.9 (range 0 to 16) and for the pain free status was 1.6 ± 2.4 (range 0 to 10).

Figure 3 – Mig-SCog total score for Migraine, Non-headache pain and Pain-free



Legend: vertical line within boxes represents the median; boxes represent the 25th and 75th percentile and T-lines the minimum and maximum values; * Difference between Migraine and Non-Headache pain is significant (p<0.0003); ** Difference between Migraine and Pain Free is significant (p<0.0003)

Average scores of Mig-SCog differed between situations (p< 0.0001 by the Friedman test). The Friedman test for each of the Mig-SCog items showed similar results, documenting that median scores in each item differed between migraine, non-migraine pain and pain free (p<0.0001).

Post-hoc comparison of means with multiplicity-adjusted p-values showed that the average Mig-SCog score was higher for migraine, compared to the pain-free status (p<0.0006) and to the non-headache pain (p<0.0006). (Figure 3).

All items presented had higher scores for migraine compared to the pain free status (p<0.003) and to non-headache pain (p<0.0003). (Table 4).

Table 4 – Pairwise comparison of Mig-SCog scores in Migraine, Non-headache pain and Pain free

	Migraine (Av ± sd)	**Non-Headache Pain** (Av ± sd)	**Headache Free** (Av ± sd)
Item 1 (confused)	0.78*,** ± 0.755	0.13 ± 0.423	0.15 ± 0.359
Item 2 (speed)	1.43*,** ± 0.633	0.81† ± 0.500	0.15 ± 0.399
Item 3 (route)	0.85*,** ± 0.723	0.39† ± 0.576	0.12 ± 0.370
Item4 (thinking)	1.25*,** ± 0.659	0.24 ± 0.495	0.24 ± 0.464
Item 5 (thread of thoughts)	1.21*,** ± 0.708	0.22 ± 0.487	0.27 ± 0.510
Item 6 (understand)	0.58*,** ± 0.762	0.10 ± 0.354	0.07 ± 0.265
Item 7(organizing sentences)	0.76*,**± 0.761	0.16 ± 0.447	0.18 ± 0.386
Item 8 (naming people)	0.36*,** ± 0.569	0.15 ± 0.359	0.21 ± 0.478
Item 9 (naming objects)	0.43*,** ± 0.609	0.18 ±0.386	0.22 ±0.487
Mig-SCog Total Score	7.66*,** ± 4.574	2.39 ± 2.954	1.61 ± 2.316

Legend: *Scores were higher for Migraine compared to Non-headache pain (p<0.0003); **Scores were higher for Migraine compared to Headache free (p<0.0003);

3. Comparison of Migraine during and in-between attacks

Fifty four patients were included in this part of the study. Sixteen patients (29.6%) were excluded because they completed only one of the evaluations, two patients failed to complete the baseline evaluation, while the other 14 failed to return for evaluation during an attack. The total study population consisted of 38 patients (1 male, 2.6%), all right-handed, 4 having migraine with aura (10.5%). The average age was 37.1 ± 10.1 years (range 21 to 63 years) with 13.8± 4.8 years of education (range 4 to 22 years).

Nineteen patients (50%) had 1-4 attacks monthly, most lasting 4 to 24h (47.4%) and of moderate to severe intensity (100%). Seven participants(18.4%) were receiving migraine prophylactics (amitriptyline 2, topiramate 2, propranolol 2 and 1 on propranolol and amitriptyline). The average HIT-6 score was 62.9 ± 6.2 (range 45 to 76). The index attack had an average duration of 11.4 ± 14.0 hours (range 30 minutes to 67.8 hours) at the time of the evaluation and mean attack intensity was 6.2 ± 1.7 (range 3 to 10) on a visual analogue scale (VAS). Average elapsed time between baseline and attack evaluation was 126.9 ± 104.1 days (range 26 to 418 days) – an average of about 4 months.

Average Mig-SCog total score in the baseline evaluation was 7.4 ± 4.3, range 1 to 18, and in the attack evaluation was 6.8 ± 4.1, range 0 to 17 (p= 0.26 by the sign test).

Comparison of median scores of each of the Mig-SCog items between attack and baseline also failed to reveal statistical differences.

The intraclass correlation coefficient (ICC) for the average Mig-SCog score was 0.805 ($p<0.0001$). The ICCs for each item were 0.631 (item 1, $p=0.002$), 0.627 (item 2, $p=0.002$), 0.657 (item 3, $p=0.001$), 0.769 (item 4, $p<0.0001$), 0.518 (item 5, $p=0.015$), 0.735 (item 6, $p<0.0001$), 0.664 (item 7, $p=0.001$), 0.623 (item 8, $p=0.002$) and 0.659 (item 9, $p=0.001$).

DISCUSSION

The Mig-SCog is a questionnaire developed to evaluate subjective cognitive dysfunction related to migraine that is self-rated and extremely short, which makes it usable in routine clinical practice. This study has demonstrated that the impact of subjective cognitive symptoms occurring in migraine and tension-type headache is not the same - migraine patients have higher total scores using this instrument than do tension-type headache patients. Not all of the 9 items of the Mig-SCog showed differences between the two diagnosis– items related to naming (items 8 and 9) were similar, suggesting that naming difficulties happen nearly as often in migraine as in tension-type headache patients. These items also had the lowest average scores of all items (below 0.5 in both diagnosis) implying a small impact of this symptoms, irrespective of headache diagnosis. This is in accordance with the fact that language abilities are relatively resistant to brain dysfunction. The two other language items (6 and 7) of the Mig-SCog also presented lower scores both in migraine and tension-type headache patients than did items related to executive functioning (1 to 5) yet with an identifiable difference between diagnosis.

Migraine patients evaluating their difficulties during non-headache pain or in their pain-free status using the Mig-SCog also scored items 8 and 9 (naming) lower than all other items but still higher than when with non-headache pain or being pain free, reinforcing that these complaints occur more often during migraine but its expression is not as strong as that of the remaining items of the Mig-SCog. Subjective language complaints are less frequent than memory complaints in the general population, and less often related to age; within language complaints, word finding difficulties seem to be much more frequent than proper name retrieval(207), which can explain why naming

were the items with lowest scores. Nevertheless, subjective language complaints bear some correlation to mild impairment in objective testing not only of language, but also of learning and attention (207).

The executive items had the highest differences between patients with the diagnosis of migraine and tension-type headache, especially items 2 (performing tasks at the normal speed), 3 (difficulty following a route), 4 (difficulty thinking) and 5 (trouble maintaining the tread of your thoughts). All these items also had presented higher scores when comparing the migraine status to non-headache pain or being pain free. An interesting observation of this study was that in migraine patients, items 2 and 3 scores were different between non-headache pain and pain free status- Based on this observation we can speculate that speed and attention difficulties may relate to pain by itself(208), therefore possibly unspecific for migraine, although our study design does not allow the verification of this hypothesis. Conversely, item 2 had the highest scores in migraine, tension-type headache and non-headache pain but not in pain free status, which can lead to the speculation of being related to pain.

Bearing in mind that subjective cognitive complaints are found to correlate with objective deficits in neuropsychological tests in the general population (207, 209), these findings corroborate previous documentation of reversible pre-frontal and executive difficulties during migraine attacks (60, 96, 98, 100, 102, 109, 159). Several executive measurements - such as trail B and Wisconsin(59), alternate finger tapping (210), visual-spatial SWITCH task(203) and in the Boston Scanning Test and Controlled Oral Word Association Test (but not in Trail B) (211) – documented a decline in migraineurs compared to controls. The differences were related to length and severity of the disease(59), to a reduced middle frontal gyrus GM density(203) but not to the presence of white matter lesions on MRI(211), suggesting a reversible cortical involvement during migraine without aura attacks. The migraine attack has also been shown to negatively influence memory tests, namely in visual memory (60, 96, 97), verbal memory and learning (100, 109), that could be related to an increase of baseline hyperexcitability of the anterior temporal pole during the migraine attack, as documented by fMRI(152).

A negative influence on attention tasks, with lower accuracy and speed of performance can also occur during tension-type headache attacks, that were irrespective of task complexity or task-specific mechanisms and unrelated to pain intensity(208).

Kuhajda showed that having an headache (migraine or tension-type) during a recognition task interferes with its performance while having headache during an encoding task does not interfere with performance but with speed of performance, suggesting again an attention deficit (99). The effect of experimental pain in healthy adults' attention processes has also been demonstrated, especially in those aspects most essential for performance on complex tasks(212). A wide range of chronic pain disorders has been studied for evidence of cognitive dysfunction and consistent findings include deficits in attention (especially on attention switching and attentional interference), slower reaction times, increase impulsivity and difficulties in complex executive tasks, impairments that do not seem to follow a disease-specific pattern(89). The cognitive impairment associated with pain may have neuroanatomical grounding as structures of the "pain matrix", such as the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC), are also crucial cognitive relay stations, especially for executive functioning. There are also neurochemical substrates, as several neurotransmitter systems are commonly involved in both pain processing and cognition(89).

In the third part of our study we demonstrated that answers to the Mig-SCog are reliable, as scores within the attack reproduced those given while pain free and report to the patients' usual attacks. This implies that even within a given time difference when reporting, patients are still able to report impairment occurring during their attack accurately. This does not imply that Mig-SCog is a reliable score for real-time subjective cognitive symptoms intensity of any given attack, as we did not test this aspect of the scale.

The major limitation of the first part of our study was the population differences between the migraine and TTH groups – the migraine group had higher proportion of females, were slightly younger (3.5 years) and had a slightly higher literacy (almost 1 year), age and literacy being known to influence cognitive performance and probably awareness of cognitive difficulties. Disease duration was higher in the migraine group (by 7 years) and migraine patients were on headache prophylactics more often than tension-type headache patients, treatments that can also influence perception of cognitive status. Nevertheless regression analysis failed to identify any co-variable that had influence on Mig-SCog score difference between diagnoses, including gender, age, literacy, and disease duration, presence of other medical conditions, current

medication and current prophylactic medication. The use of topiramate was noted in 18% of migraineurs in this study. Complaints of cognitive dysfunction with topiramate in healthy individuals (213) and migraine patients (145) were corroborated by a documented decrease in attention, memory and psychomotor speed in previous studies. This could be an important bias in our sample, but regression analysis failed to relate the use of topiramate to a higher score in Mig-SCog. Possible explanations include a coincidental low incidence of cognitive effects in the current sample, a dilution of these changes with effects of other treatment with more subtle influence on cognition (as other anti-epileptic drugs) or a resistance of this scale to cognitive complaints related to topiramate use. This study was not designed nor powered to clarify this issue. Due to the inclusion of highly educated individuals, our results cannot be extrapolated to lower literacy levels.

The Mig-SCog total score had an AUC of 0.835 for the diagnosis of Migraine, which corroborated its specificity for Migraine, when compared to tension-type headache. None of the items of the Mig-SCog taken individually had a high power of prediction for the diagnosis of migraine. It is important to bear in mind that this instrument was not built as a diagnostic tool, so the performance analysis calculated in this study had the sole aim of confirming the utility of the Mig-SCog for migraine patients.

In conclusion, Mig-SCog is a fast, inexpensive and easy to apply instrument that is able to quantify subjective cognitive symptoms specific for migraine in a consistent way even when reporting attacks occurring in the past, and could be useful as a clinical aid to establish attack-related disability assessment, may be of help in migraine diagnosis and could be considered as an endpoint measure in clinical trials in migraine.

4. Objective Cognitive Dysfunction during Migraine Attacks

OBJECTIVE COGNITIVE DYSFUNCTION DURING MIGRAINE ATTACKS

CHAPTER FOREWORD

In this chapter the interest is focused on the documentation of objective cognitive dysfunction during migraine attacks, to substantiate patients' perceptions of cognitive difficulties.

Neuropsychological tests are clinical and research tools that provide standardized measurements of cognitive performance, being widely available and applicable with minimum resources. A systematic review of the medical literature was first ensued, searching for evidence of attack-related cognitive impairment in migraine, defined as a decline in neuropsychological testing during a migraine attack, compared to headache-free performance. Data obtained had little consistency, probably a result of different study methodologies, small sample sizes, different neuropsychological batteries and the presence of bias. Nevertheless, most of the studies were positive demonstrating an attack-related impairment, probably due to executive dysfunction.

A prospective two-period randomized crossover study was designed trying to improve the knowledge gap on this topic. The study design and inclusion criteria had the objective of minimizing bias, the battery used was extensive and detailed and the included sample size was adequate. Despite having had a high attrition rate that limited the statistical power, results were still consistent with the existence of reversible cognitive dysfunction during attacks, especially in reading and processing speed, verbal memory and learning.

Having an objective measure of the impact of cognitive dysfunction during attacks is relevant for clinical practice and essential in clinical trials of acute attack treatment, yet an extensive battery of neuropsychological tests is time consuming and therefore not adequate nor practical. A shorter battery was assembled, focusing on executive and language domains, to those purposes. The performance on this battery was tested in interictal migraine patients and controls and in repeated applications, to identify the

predictable score intervals for which a change in test scores in repeated applications could be judged clinically meaningful.

Cognitive performance can also be studied by functional brain imaging, which relies on the identification of blood flow changes in certain contexts. Cortical perfusion changes are well documented in the aura phase of migraine with aura attacks, a clinical phenomenon though to be related to an intense self-propagating wave of cortical (neuronal and glial) depolarization followed by a longer lasting wave of neuronal inhibition. The headache phase of migraine often follows the aura yet cortical perfusion abnormalities occurring during the headache phase or in migraine without aura are inconsistent in the few studies published with different techniques; if present during the headache those changes reflecting cortical hypometabolism could relate to cognitive symptoms occurrence.

Arterial spin labeling magnetic resonance imaging (ASL-MRI), a non-invasive and accurate study of brain perfusion that is sensitive to changes in the capillary level, was used for the first time to scan migraine patients during a spontaneous occurring untreated migraine without aura attack and again in the headache-free status. Global and regional cortical perfusion was found to be identical in both situations reflecting that cortical metabolic changes, if present during attacks, fall whitin the range of physiological variation.

Nevertheless, brain normal responses could be disrupted by the migraine attack as some brain areas (particularly the anterior cingulate and the frontopolar cortex) which are effective centers of executive function are recruited and active during migraine attacks(29, 53, 153, 214, 215). To test this hypothesis, evoked brain activation using a working memory paradigm (the N-Back) was studied using blood-oxygen level dependent functional magnetic resonance imaging (BOLD-fMRI) in migraine patients during a spontaneous occurring untreated migraine without aura attack and again in the headache-free status. In this study, the migraine attack was not associated with any difference in brain activation patterns or areas, compared to the headache free status so it was not possible to identify the brain processes underlying patients' symptoms.

Assessment of cognitive dysfunction during migraine attacks:

A systematic review.

Gil-Gouveia R, Oliveira AG, Martins IP.
Assessment of cognitive disorders during migraine attacks: A systematic review.
Journal of Neurology 2015 Mar;262(3):654-65. Impact Factor: 3.84

ABSTRACT

Background: Patients consistently report cognitive impairment during migraine attacks, yet the documentation of such dysfunction by neuropsychological evaluation has lacked similar consistency. This incongruence may be due discrepant study designs, assessment tools and small samples sizes.

Objective: To search for evidence of decline in cognitive functions during a migraine attack, compared to headache-free performance. The secondary objective was to determine if the eventual decline had a consistent neuropsychological pattern.

Methods: Systematic review of the medical literature using PubMed and Cochrane library databases without limitations or restrictions from inception to March 2014, using the search terms "migraine", "cognition", "neuropsychological". We included studies in episodic migraine that had a neuropsychological evaluation performed during an attack.

Results: From 1023 titles screened, a total of 10 articles met criteria for inclusion and were fully reviewed. Only five of these studies, comprising a total of 163 individuals, had enough data to allow an appraisal of the study question. All five studies were positive in documenting some type of reversible cognitive impairment during the migraine attack. The pattern of cognitive impairment most often documented was of executive dysfunction, but the presence of bias induced by the choice of tests and of small samples prevents this finding from being conclusive.

Discussion: This review supports the existence of reversible cognitive dysfunction during the migraine attack, corroborating patients' subjective descriptions. Further work is needed to establish the pattern of cognitive dysfunction, their underling pathophysiological mechanisms and the impact of these symptoms in migraine-associated disability.

INTRODUCTION

Cognitive symptoms during migraine attacks were first reported by the roman Aulus Cornelius Celsus (25–50 A.D.) as "*alienation of the mind"* occurring *"in addition to intolerable pain …. blurred vision, vomiting…"*(9). More detailed descriptions of subjective cognitive symptoms occurring during migraine attacks are available since 1873, by Edward Liveing(11), such as *"...impairment of memory and in confusion and incoordination of ideas..", ".. confusion of thought..", "…unable to collect his thoughts…", "…feeling silly…", "…losing their senses…".* An inventory of such symptoms has been detailed in diary studies of migraine premonitory symptoms in clinical samples of migraineurs (22-25, 27, 121), although most of these studies failed to evaluate the persistence of these symptoms into the headache phase. Subjective cognitive symptoms are also included in questionnaires of migraine-related disability assessment or of treatment outcomes(95, 133, 136, 156). A specific subjective scale has been developed for evaluating and quantifying the presence of subjective cognitive dysfunction during the migraine attack(118). Due to the consistency of these subjective reports, the most likely pattern of neuropsychological impairment during migraine attacks would relate to the cognitive domains of executive functioning, language and multidomain requiring complex tasks (22-25, 27, 118, 121) and it is very likely that these cognitive difficulties contribute to migraine related disability (95, 133, 136, 156). Reversible neuropsychological impairment could be related to changes in brain function during migraine attacks, as ictal changes have been documented in functional neuroimaging studies involving the cortical structural such as the cingulated cortex, insula, prefrontal cortex and temporal lobe(101).

The suspicion of a possible increased risk of long-term or progressive cognitive decline in migraine patients was based on these subjective cognitive complaints, taken together with the evidence of increased prevalence of silent brain lesions in migraine(216). Large reviews of several cross-sectional studies and of large prospective epidemiological studies evaluating cognitive performance of migraine patients outside attacks failed to document any relevant interictal cognitive dysfunction of otherwise healthy migraine patients(105), as well as of any association between migraine and progressive cognitive decline(217).

Despite abundant evidence of the occurrence of subjective cognitive difficulties during the attack, objective data supporting ictal or attack-related cognitive dysfunction is scarce, heterogeneous and difficult to analyze due to small sample sizes and to different study designs.

In the present study we aimed to perform a systematic literature review with the aim of identifying and summarizing existing information on ictal cognitive functioning (i.e., *during* the migraine attack) measured by formal neuropsychological testing. Specifically, our questions were: Is there evidence of decrease in any cognitive function during a migraine attack, when compared to headache-free performance? If so, is there any cognitive domain or neuropsychological pattern that is consistently found, in the context of migraine headache attack?

METHODS

Search Strategy

Potentially eligible studies were identified through electronic databases search of Medline (through PubMed) and the Cochrane Library from inception to March 2014. We did not include any limitations nor restrictions. The search used the free text terms “migraine” AND “cognition”, “migraine” AND “neuropsychological”. The thesaurus terms used in these searches were "Headache" OR "Headache Disorders" OR "Migraine Disorders" OR "Migraine with Aura" AND "Cognition" OR "Cognition Disorders” AND “Neuropsychological”.

Study Selection and Data Collection

Titles and abstracts were screened for relevance, studies were included if they referred to cognitive evaluation in headache disorders. Studies were then excluded if they reported (1) cognitive evaluation on other headache types than episodic migraine (including hemiplegic migraine, chronic migraine, medication overuse, post-traumatic headache); (2) cognitive effects of treatments used in migraine patients; (3) if they had cognitive endpoints unrelated to neuropsychological assessment; (4) if they failed to evaluate migraine patients during the pain or post-ictal phase of a migraine attack; (5) if the cognitive evaluation was performed during the aura phase of the attack; or if (6) reported on individual cases, were letters or comments. References of relevant papers

and references of reviews were also screened with the same criteria and selected papers were retrieved and evaluated thought the same process. Any disagreements were resolved by consensus.

Data extraction and analysis

A table was constructed to summarize relevant results from the studies selected. Study designs, objectives and outcome measurements were discrepant and not amenable to quantitative analysis. Data was classified and analyzed qualitatively. Ethics committee authorization was not required as this study reviewed previously published data.

RESULTS

The study flow is depicted in figure 1. A total of 10 papers met the eligibility criteria for review and their characteristics are depicted in table 1; one of these papers was an abstract from a poster presentation(100). One of the included papers had also an abstract from a poster presentation with data from the same sample, that was excluded due to duplicate data(60, 102).

The objectives, and therefore designs, of the studies were different – three studies analyzed therapeutic interventions and used cognitive evaluation as a therapeutic endpoint (96, 97, 102) and all of these were positive in documenting a cognitive decline during the migraine attack, when compared to headache-free evaluations, with recovery of cognitive performance after the therapeutic intervention (sumatriptan in three studies, sumatriptan with naproxen in one study). Two of these studies were uncontrolled open label studies (60, 96, 102); the remaining study, by Edwards(97), was a double-blind, placebo controlled study that failed to establish differences of the active arm from placebo, as both improved cognitive performance after intervention.

STUDY FLOW

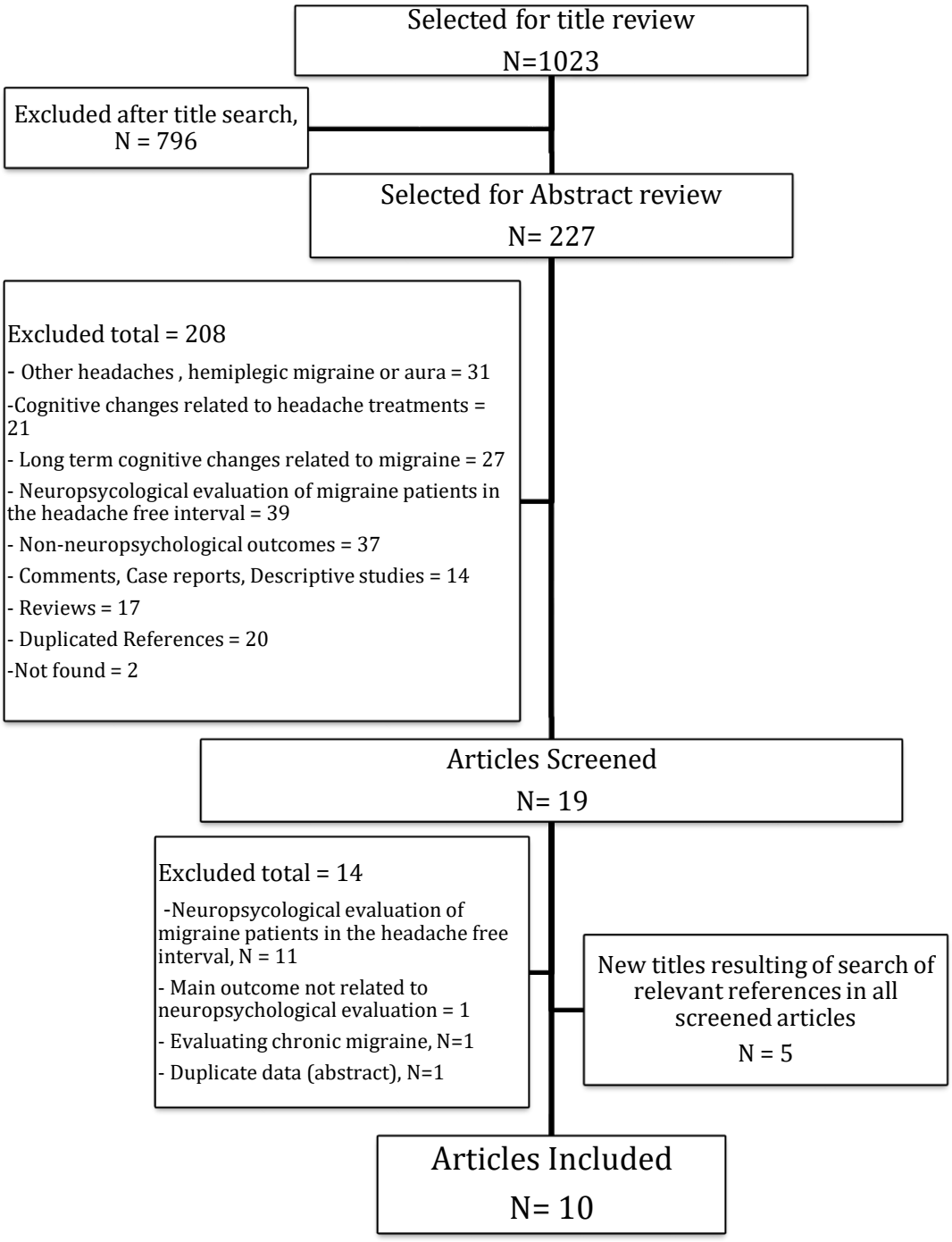

Selected for title review
N=1023
Excluded after title search,
N = 796
Selected for Abstract review
N= 227
Excluded total = 208
- Other headaches , hemiplegic migraine or aura = 31
-Cognitive changes related to headache treatments = 21
- Long term cognitive changes related to migraine = 27
- Neuropsycological evaluation of migraine patients in the headache free interval = 39
- Non-neuropsychological outcomes = 37
- Comments, Case reports, Descriptive studies = 14
- Reviews = 17
- Duplicated References = 20
-Not found = 2
Articles Screened
N= 19
Excluded total = 14
-Neuropsycological evaluation of migraine patients in the headache free interval, N = 11
- Main outcome not related to neuropsychological evaluation = 1
- Evaluating chronic migraine, N=1
- Duplicate data (abstract), N=1
New titles resulting of search of relevant references in all screened articles
N = 5
Articles Included
N= 10

Table 1 – Summary of included studies and Main findings

STUDY DETAILS		Neuropsychological Evaluation	Main Findings
Author, Year, reference	Design / Objective / Sample Size		
Edwards, 2013**(97)**	Double-blind, placebo-controlled, cross-over comparison of cognitive function of migraine patients (N=30) in headache-free status with onset of migraine, prior to treatment and 1 and 2 hours after treatment (sumatriptan-naproxen)	Mental Efficiency Workload Test (MEWT) (computerized test with 4 subtests): (1) simple reaction time (SRT); (2) procedural reaction time (PRT); (3) matching to sample (M2S); (4) pursuit tracking (PT)	. Decline in all tests in untreated migraine compared to baseline . Study drug improved SRT and PRT, no difference from placebo
Koppen, 2011**(218)**	Observational case-control study of cognitive performance of migraine patients (N=16) and matched controls (N=18) in the first headache morning after an attack and 1 and 12 days after the first evaluation.	Three Computerized Tests: (1) Perceptual organization (global-local) task; (2) Attentional Network Task (ANT); (3) N-back task	. No cognitive decline in the post-ictal phase . Perceptual organization of local and global visual stimuli different in migraine and controls, in all evaluations . ANT and N-Back without differences
Kuhajda, 2002**(99)**	Observational longitudinal study of headache patients (N=80, migraine and tension-type headache together) performance on a cognitive task while in pain and pain-free	A computerized test of memory evaluating: (1) encoding (2) retrieval (3) response time	.Headache during encoding had no influence on memory performance but resulted in slower response times . Having headache during recognition negatively influenced results
Farmer, 2001**(96)**	Open-label, single-arm study of cognitive function of migraine patients (N=28) in headache-free status and onset of migraine prior to treatment and 15, 45, 75, 105 and 135 minutes after treatment (nasal sumatriptan).	Headache Care Center-Automated Neuro-psychological Assessment Metrics (HCC-ANAM)-(computerized test with 4 subtests): (1) simple reaction time (SRT); (2) continuous performance test (CPT); (3) matching to sample (M2S); (4) mathematical processing (MP)	. Decline in all tests in untreated migraine compared to baseline . Study drug returned all measures to baseline or near baseline levels
Farmer, 1999 & 2000 **(60, 102)**	Open-label, single-arm study of cognitive function of migraine patients (N=10) in headache-free status, onset of migraine prior to treatment and 15, 30 and 45 minutes after treatment (sc sumatriptan)	Headache Care Center-Automated Neuro-psychological Assessment Metrics (HCC-ANAM)-(computerized test with 4 subtests): (1) simple reaction time (SRT); (2) continuous performance test (CPT); (3)	. Cognitive efficiency (number of correct answers per minute) declined in all tests in untreated migraine compared to baseline . Study drug returned all measures to baseline

		matching to sample (M2S); (4) mathematical processing (MP)	
Meyer, 2000**(98)**	Observational cohort study of cognitive performance of migraine (N=65, 17 with aura), cluster headache (N=7) and chronic daily headache (N=5) with repeated evaluations in intervals of 3 to 12 months over a 10-year period, sometimes during pain, others while pain-free.	Non-computerized tests: (1)Mini-Mental Status Examination (MMSE) (2) Cognitive Capacity Screening Examination (CCSE)	. CCSE and MMSE scores decreased significantly in evaluations during headache and returned to normative levels when headache-free. . Findings were similar in all headache types evaluated
Mulder, 1999**(159)**	Open label case-control study of cognitive performance of migraine patients (N=30, 10 with aura) and matched controls (N=30) in headache free status and two evaluations 30h into two treated attacks, one treated with NSAID and another with sumatriptan	Neurobehavioural Evaluation System (NES2) (computerized test with 4 subtests): (1) reasoning; (2) simple reaction time (3) switching attention; (4) finger-tapping; (5) Hand-eye coordination; (6) continuous performance pictures and letters; (7) color-word; (8) serial digits; (9) symbol-digit substitution; (10) horizontal addition; (11) visual digit span; (12) pattern comparison and memory	. Headache free migraineurs with aura in were slower than controls in symbol digit substitution, continuous performance and color word tests . Post-attack evaluations failed to document differences to headache free status irrespective of treatment used
Bell, 1999**(219)**	Observational cross-sectional comparative study of cognitive performance of frequent headache patients (N=20) and frequent non-headache pain (N=20) and Mild Traumatic Brain Injury patients (MTBI, N=20) evaluated once, in a mild pain day	Non-computerized tests: (1) Logical Memory; (2) Verbal Paired Associates and Visual Reproduction (WMS-R)M (3) Trail Making test; (4) Stroop Test; (5) Block Design (WAIS-R); (6) Controlled Oral Word Association Test; (7) Paced Auditory Serial Addition Task (PASAT); Analysis of 3 neuro-psychological indexes: cognitive efficiency, memory, visual-perception ability	. MTBI groups had lower performance on memory index . No significant cognitive difference between the headache and non-headache pain patients, with performance within normal expectations
Black, 1997**(100)**	Observational cohort study of cognitive performance of migraine (N=30) in 3 repeated evaluations, two in headache free period (office and phone-based) and one during a migraine attack.	Non-computerized tests evaluating speed of processing, immediate and sustained attention, verbal learning, visuo-constructional abilities	. Early stages of the attack showed decreased performance in sustained attention and verbal learning.
Mazzucchi, 1988**(103)**	Observational case-control study of cognitive performance of migraine with aura patients (N=42) and matched controls (N=20) in headache free status and within 24h of a migraine with aura attack	Computerized Posner Paradigm, calculating visual reaction times (RT) analyzing inter-hemispheric differences	. All RTs increased during attack when compared to baseline . Migraineurs outside the attack were identical to controls

The other evaluated studies were all observational. Three were case-control studies comparing baseline headache-free cognitive performance to controls (cross-sectional evaluation outside the attack) and comparing post-ictal to baseline cognitive performance in patients (follow-up study with repeated measures) (103, 159, 218). These studies evaluated the post-ictal phase of the migraine attack. Only one had pre-defined treatment drugs (sumatriptan and NSAIDs) and all subjects had evaluations after treating the attacks with both drugs(159). In these cross-sectional analysis cognitive performance in the headache-free period of migraine patients was identical to controls in one study(103) and different in two(159, 218). The comparative analysis of repeated evaluations in the headache free and post-ictal period of migraine patients was positive in one study(103), that documented slower reaction times in the post-ictal compared to the headache-free period, and negative in two studies(97, 159).

Of the four remaining articles, three were follow-up studies analyzing cognitive performance in repeated evaluations by comparison of headache-free status with untreated pain(98-100). One of these studies included several headache types (migraine with and without aura, cluster and chronic daily headache) and performed a comparative analysis of performance at baseline and during pain, between diagnosis(98); one other study included migraine and tension-type headache patients together in one "headache" group and compared their performance on a cognitive task in their headache-free status with the untreated pain status(99). All three studies were positive for cognitive dysfunction during the attack compared to headache-free status, the study comparing several types of headache found no differences between headache diagnosis(98, 100). The last study is a cross-sectional comparative study of migraine patients while in mild pain with non-headache pain and mild traumatic brain injury patients, that failed to find differences in cognitive performance between headache and non-headache pain(219).

Most of these studies had small or medium sample sizes, varying from 10 (60, 102) to 65 (98) migraine subjects evaluated, all together 333 headache patients (mostly migraine, including some tension-type headache) were included (96-100, 102, 103, 159, 218, 219).

Assessment tools were heterogeneous (table 2). Six studies used computerized tests, including three batteries: the Mental Efficiency Workload Test (MEWT) (97), that is an abbreviated version of another battery also used, the Headache Care Center–Automated Neuropsychological Assessment Metrics (HCC-ANAM) (60, 96, 102); both of these batteries focused mainly on processing speed, visual-motor abilities and working memory. The third battery, the Neurobehavioural Evaluation System (NES2)(159), is more extensive but also focus on executive measures (reaction time, motor speed and hand-eye coordination, attention and working memory). Other computerized tests used included the Posner paradigm(103), other executive tasks (N-back and attentional network) tasks(218), a perceptual organization of visual stimuli test(218), and a memory test (99).

Non-computerized tests were used in 3 studies. One used multidomain screening tests (MMSE and CCSE)(98), another used an extensive test battery including memory, executive and visual-perception tests(219), and the third (an Abstract from a poster presentation) did not specify the tests used(100).

Table 2 – Neuropsychological tests and Cognitive domains

Cognitive Domain		Neuropsychological tests	Result
EXECUTIVE FUNCTIONS	Attention	**1.Comparing "migraine" with "headache free"**	
		Computerized: - MEWT (97) (procedural reaction time; pursuit tracking)	↓
		- HCC-ANAM(60, 96, 102) (continuous performance test)	↓
		Conventional: - Unspecified test (100)	↓
		2.Comparing "postdromal migraine" with "headache free"	
		Computerized: - NES2 (159) (continuous performance pictures and letters; color-word)	=
		- Posner Paradigm (103)	↓
		- Attentional Network Task (218)	=
		3.Comparing "migraine" with "non-headache pain"	
		Conventional: -Stroop test (219)	=
		-Trail Making test (219)	=
		-Paced Auditory Serial Addition Task(219)	=
	Processing speed	**1.Comparing "migraine" with "headache free"**	
		Computerized: - MEWT (97) (simple reaction time)	↓
		- HCC-ANAM(60, 96, 102) (simple reaction time)	↓
		Conventional: - Unspecified test (100)	↓

		2.Comparing "postdromal migraine" with "headache free" Computerized: - NES2 (159) (simple reaction time; switching attention) - Posner Paradigm (103) **3.Comparing "migraine" with "non-headache pain"** Conventional: -Stroop test (219) -Trail Making test (219) -Paced Auditory Serial Addition Task(219)	= ↓ = = =
	Working Memory	**1.Comparing "migraine" with "headache free"** Computerized: - MEWT (97) (matching to sample) - HCC-ANAM(60, 96, 102) (matching to sample) **2.Comparing "postdromal migraine" with "headache free"** Computerized: - NES2 (159) (serial digits; symbol-digit substitution) - N-back task(218) **3.Comparing "migraine" with "non-headache pain"** Conventional: -Paced Auditory Serial Addition Task(219)	↓ ↓ = = =
	Reasoning	**2.Comparing "postdromal migraine" with "headache free"** Computerized: - NES2 (159) (reasoning);	=
	Mental Flexibility	**3.Comparing "migraine" with "non-headache pain"** Conventional: -Stroop test (219) -Trail Making test (219)	= =
	Motor Function and Speed	**1.Comparing "migraine" with "headache free"** Computerized: - MEWT (97) (pursuit tracking) **2.Comparing "postdromal migraine" with "headache free"** Computerized: - NES2(159) (finger-tapping; Hand-eye coordination)	↓ =
	Calculation abilities	**1.Comparing "migraine" with "headache free"** Computerized: - HCC-ANAM(60, 96, 102) (Maths) **2.Comparing "postdromal migraine" with "headache free"** Computerized: - NES2(159) (horizontal addition) **3.Comparing "migraine" with "non-headache pain"** Conventional: -Paced Auditory Serial Addition Task(219)	↓ = =
PERCEPTION & MOTOR	Perceptual Organizatio n	**2.Comparing "postdromal migraine" with "headache free"** Computerized: - Global-local Task(218);	=
	Visual Perception	**2.Comparing "postdromal migraine" with "headache free"** Computerized: - NES2 (159) (pattern comparison) **3.Comparing "migraine" with "non-headache pain"**	=

		Conventional: - Visual Reproduction I (Wechsler Memory Scale-Revised) (219) - Block Design (Wechsler Memory Scale-Revised) (219)	= =
	Visuo-motor processing	**1.Comparing "migraine" with "headache free"** Computerized: - MEWT (97) (simple reaction time) - HCC-ANAM(60, 96, 102) (simple reaction time) Conventional: - Unspecified test (100) **2.Comparing "postdromal migraine" with "headache free"** Computerized: - NES2 (159) (simple reaction time) - Posner Paradigm (103) **3.Comparing "migraine" with "non-headache pain"** Conventional: -Trail Making test (219)	↓ ↓ ↓ = ↓ =
MEMORY	Visual Memory	**1.Comparing "migraine" with "headache free"** Computerized: - MEWT (97) (matching to sample) - HCC-ANAM(60, 96, 102) (matching to sample) **2.Comparing "postdromal migraine" with "headache free"** Computerized: - NES2 (159) (pattern memory) **3.Comparing "migraine" with "non-headache pain"** Conventional: -Visual Reproduction II (Wechsler Memory Scale-Revised) (219)	↓ ↓ = =
	Logical Memory	**3.Comparing "migraine" with "non-headache pain"** Conventional: -Logical Memory (Wechsler Memory Scale-Revised) (219)	=
	Verbal Memory	**1.Comparing "migraine" with "headache free"** Conventional: - Unspecified test (100) **3.Comparing "migraine" with "non-headache pain"** Conventional: - Verbal Paired Associates (Wechsler Memory Scale-Revised)(219) - Controlled Oral Word Association Test (Multilingual Aphasia Examination) (219)	↓ = =
	Long-term episodic memory	**1.Comparing "migraine" with "headache free"** Computerized: - Memory (encoding/retrieval)(99)	=
	Multidomain (total score analysis)	**1.Comparing "migraine" with "headache free"** Conventional: -Mini-Mental Status Examination (MMSE) (98) - Cognitive Capacity Screening Examination (CCSE) (98)	↓ ↓

Legend: ↓ Decreased performance during the "migraine attack" or "postdromal migraine" compared to headache free ; = Equal performance between "migraine attack" or "postdromal migraine" and "headache free" or "non-headache pain".

In some of the studies the authors attempted to control for possible confounding factors that could influenced cognitive performance, mostly in their study design. Most studies excluded severe medical conditions(97), neurological disorders (ex. epilepsy, stroke and traumatic brain injury) and substance abuse (96, 159, 218, 219), some precluding frequent headache (96, 218), complex auras (96) and current headache prophylactics (159). In two studies headache prophylactics were allowed (98, 99). Mood disorders were also excluded in some studies (99, 218) and controlled for in one(219) and none of the studies mentioned if the migraine attack evaluated had had aura or not, with the exception of one study that was specifically designed to evaluate migraine with aura(220). The practice effect of repeated neuropsychological testing was not controlled for in most of the studies, some studies had the first test presentation while headache free, followed by the attack evaluations within an unspecified time frame(60, 96, 97) while others did not specify the order or evaluations(98, 220). In one study alternate test forms were applied in trying to minimize this bias(100), in two studies the same attempt was made by the use of a matched control group who underwent the same neuropsychological protocol(159, 218) and in one study the inclusion order was randomized(99).

The headache status of evaluations also varied between studies – in three studies the attack evaluation was exclusively made in the postdromal phase (either after treatment or after spontaneous headache resolution) and not during the headache (159, 218, 220). In one study there was no baseline (headache free) evaluation(219) and in another study the baseline evaluation allowed the presence of mild headache and it also failed to discriminate between migraine and tension-type headache patients (99). The majority of studies did not contain information about criteria for defining the "headache-free" nor the "headache" status (60, 96-98, 100, 219).

Taking all the studies globally, 7 documented a decline in the selected neuropsychological evaluation during the untreated migraine attack, when compared to the baseline headache-free status (60, 96-100, 102, 103). Three were negative, two

tested the post-ictal phase of the attack (after successful treatment)(159, 218) and one had no baseline evaluation and compared migraine with non-headache pain(219).

The pattern of cognitive decline documented was mostly of executive dysfunction (96, 97, 99, 100, 102, 103), with decreased performance in attention, processing speed and working memory tasks during the untreated attack, but also of memory (visual memory (60, 96, 97, 102). and verbal learning(100)). One study only analyzed global cognitive functioning, so performance in specific domains was not evaluated(98).

DISCUSSION

This review had the purpose of determining if there is evidence of decrease in any cognitive function during a migraine attack, when compared to headache-free status. Although the search was limited to two databases, we did perform an extensive review of bibliographic references of all the articles screened and extended the reference search to all review papers on the topic, thus we possibly covered the vast majority of the published data available for analysis.

There were few studies published whose design allowed to answer to our question and all of them had very small sample sizes, so analysis of all studies relies on a total sample of around 351 subjects. However, in the study by Kuhajda(99), 80 patients were included as one headache group, that included migraine and tension-type headache.

Five studies included at least two evaluations, one on a headache-free status and another during the painful phase of the untreated migraine attack (96-98, 100, 102). All these studies were positive, consistently documenting a decrease in cognitive functions while in pain compared to the pain-free period, but relate to a total sample of only 163 patients. The Kuhajda study also included two evaluations and was also able to identify a difference in attention, but due to methodological issues (including migraine and tension type headache as one group and allowing mild pain in the headache free evaluation) its results were considered unreliable to answer the first study question(99). Within these limitations, we can nevertheless conclude that the published evidence is consistent with the occurrence of reversible cognitive dysfunction during the painful phase of the migraine attack, answering our first study question.

Three of the remaining studies compared the postdromal phase or the treated attack with the pain-free status that cannot, in reality, be considered when trying to answer our study question. The postdromal phase occurs after the headache phase of the migraine attack in 60 to 94% of patients, lasts 18 to 25 hours (<12h in 54% of patients) and consists of a constellation of symptoms that may include cognitive disturbances, amongst other migraine symptoms (persistent mild nausea, mild pain with head movement of physical effort etc)(25, 52). Two out of three were negative, meaning that there was no evidence of changes in cognitive performance when compared to baseline headache-free status (159, 218). One of these studies included the use of standard rescue medication sequentially with sumatriptan or NSAIDs and tested for differences between the two drugs, failing to document any (159). The other negative study did not allow the use of medication before evaluation, but this evaluation had to take place on the first headache-free morning following the attack(218). It can be argued that studying patients after successful headache treatment or following a resolved attack cannot be considered a study of the postdromal phase of migraine, but rather a comparison of treated or resolved attacks with other headache free days. Neuropsychological cross-sectional controlled studies of headache-free migraine patients are consistently negative in identifying interictal cognitive dysfunction(105), which is in turn consistent with the findings of these studies on treated or resolved attacks.

The third study, evaluating patients within 24h of the end of the last migraine with aura attack, it was not clear whether acute treatment was allowed(103). This was a positive study, documenting an increase of reaction times in the post-attack evaluation. Possible explanations include persistence of pain and/or visual impairment of the aura at the time of evaluation or the existence of a difference in post-attack brain functions between migraine with aura and migraine without aura patients. This is the only study included in this review that specifically evaluated migraine with aura; some others included aura patients within the migraine group but it was unclear if the evaluated attack had had aura (98, 159). The presence of classical aura does not seem to influence cognitive performance in migraine patients(105), although some studies of familial hemiplegic migraine documented non-progressive mild impairment of memory, attention, and some aspects of executive functions in these patients(221).

Another study that was also not able to answer our study question had an evaluation during a headache attack but failed to have a headache free evaluation(219). This was a controlled study, comparing migraine with non-headache pain, and its findings were negative, which might suggest that cognitive dysfunction during migraine is not specific to migraine but is a consequence of ongoing pain processing in the brain. Several types of chronic pain states have been documented to impair cognitive functions, mainly in the domains of attention, speed of processing, executive function, psychomotor and learning and memory(89). Nevertheless, a study on tension-type headache reproduced attention deficits occurring in experimental non-headache acute pain(208), which suggests that headache might have the same ability to influence cognitive performance in a similar way as bodily pain.

The second question of our study focused on whether there were any cognitive domains or any neuropsychological pattern of dysfunction that could be consistently identified, in the context of the acute migraine attack. Excluding one study that did not analyze specific cognitive domains(98) and the study that included both migraine and tension-type headache patients(99), we were left with 4 studies, with a total sample of around 98 patients. The most frequent finding was an attention deficit, which was found in all positive studies (60, 96, 97, 100, 102). The remaining impaired domains were processing speed and working memory in three studies (60, 96, 97, 102), visual memory in two studies (60, 97, 102), visuomotor ability(97) and verbal learning(100) in one study each. Although it might be tempting to state, in view of these results, that the main deficits are on executive functions (attention, processing speed, working memory), serious limitations prevent this generalization, the first being the *a priori* bias induced by the choice of tests to apply during the attack. Neuropsychological evaluation of patients while in pain is challenging and should be brief, especially if aiming for repeated, serial evaluations as occurred in four out of the remaining five studies (60, 96, 97, 100, 102). Given this time limitation, it becomes impossible to perform a detailed analysis of each neuropsychological domain, and choosing a more detailed evaluation of a specific cognitive domain over briefly testing a higher number of cognitive functions was the option on most of these studies, which mainly focused their evaluations on executive measures (96, 97, 100, 102), including one or other test of learning and visuomotor abilities(97, 100). One study was designed to study only one specific aspect of memory, evaluating the influence of headache in the encoding and retrieval processes(99). This

was considered a positive study, as a difference was found between conditions, but this difference was interpreted as unrelated to the memory process but rather due to an attention deficit, which corroborates the pattern found in the remaining studies (60, 96, 97, 100, 102). Although consistent with patients' subjective symptoms during the attacks(118), a similar cognitive pattern of impaired attention is also found in non-headache chronic pain(89) and tension-type headache(208), so specificity for migraine is not warranted. This review had no intention to explore the neurological subtract behind the neuropsychological dysfunction nor to compare findings of migraine attacks to other headache types or non-headache pain.

Other important limitations to the interpretation of these results are the scarce control of possible confounding factors that may influenced cognitive performance, such as anxiety and mood disorders (222, 223), prophylactic drug treatment for migraine (145) or substance abuse (224), the occurrence of aura(103) and the practice effect of repeated neuropsychological testing(225). Of the studies considered in answering our first study question(96-98, 100, 102), none had information defining the "migraine" nor the "headache free" status and none had clear information about the presence of migraine aura in the sample; only two had some inclusion restrictions(96, 97) and only one had a design that attempted to minimize the practice effect bias(100).

From all mentioned limitations and considering the small total sample of patients evaluated we conclude that there is not enough data to confirm a specific pattern of cognitive impairment of the acute migraine attack.

Summarizing, this review provides weak evidence for the occurrence of reversible cognitive dysfunction during the headache phase of the migraine attack, which subscribes patients' subjective descriptions and general clinical impression. The pattern of dysfunction suggested is mainly of a dysexecutive syndrome but the evidence to support this suggestion is frail. Further work is needed to substantiate these findings, such as testing specifically other cognitive domains during the attack and controlling for migraine related confounding factors, such as treatment effects, affective disorders and the presence or aura.

This topic has important clinical implications, as migraine attack-related cognitive dysfunction may influence patients' ability to perform in work, school and other activities, and therefore be a major contributor to migraine-related disability and

burden(15). For this reason, it is essential to better characterize the attack-related cognitive dysfunction, in order to be possible to include cognitive-related endpoints in clinical trials of acute migraine drugs.

Cognitive dysfunction during migraine attacks.

A study on migraine without aura.

Gil-Gouveia R, Oliveira AG, Martins IP.
Cognitive dysfunction during migraine attacks: A study on migraine without aura.
Cephalalgia 2015 ;35(8):662-74; Impact Factor: 4.12

ABSTRACT

Background: Cognitive difficulties contribute to patients' disability during migraine attacks and have been overlooked in migraine research. Neuropsychological studies performed during attacks have produced inconsistent findings due to design differences and limitations.

Objective: To document changes in cognitive performance of migraine patients during migraine attacks with a comprehensive battery of cognitive/behavioral tests, while controlling for potential confounders.

Method: A prospective two-period randomized crossover study compared within-subject neuropsychological evaluation in two conditions – during a naturally occurring untreated migraine attack and a headache-free period.

Results: Thirty-nine patients with episodic migraine (37 females, average 38 years-old) were included and 24 completed the study. Subjects performed worse during the attack in the majority of cognitive tests, compared to the headache-free status, and significantly so in word reading speed (p=0.013), verbal learning (p=0.01), short term verbal recall with (p=0.01) and without (p=0.013) semantic cueing and delayed recall with (p=0.003) and without (p=0.05) semantic cues. Differences found were unrelated to age, gender, literacy, condition order, interval between evaluations, anxiety, pain intensity or duration of the attack.

Discussion: Cognitive performance decreases during migraine attacks, especially in reading and processing speed, verbal memory and learning, supporting patients' subjective complaints. These findings suggest the existence of a reversible brain dysfunction during attacks of migraine without aura, which can relate specifically to migraine or be a consequence of acute pain processing by the brain.

INTRODUCTION

Migraine is a disabling disease with a significant impact in global health(177). Attacks of migraine without aura are complex biological phenomena with distinct clinical manifestations that include headache, gastrointestinal symptoms and dysfunctional modulation of sensory inputs (light, sound, smell or movement)(226, 227).

Additional attack-related symptoms, such as cognitive difficulties (95, 118, 133, 136, 156) are often reported by patients and probably reflect brain function changes during attacks. Cognitive and mental symptoms are significant contributors to patients' disability (95) and may not be relieved by effective abortive medication(158). Difficulties most often reported by patients relate to different cognitive domains such as sustained and divided attention, concentration, planning, judgment, initiative, processing speed, language and memory (98, 118). These may persist beyond the pain phase, up to the following day(158), as 80% of patients report mental tiredness, asthenia, depressed mood and concentration difficulties(25, 51) after the attack.

Cognitive dysfunction has probably been overlooked in migraine research, since data about its impact on disease-related disability is scarce and it has seldom been evaluated as a therapeutic outcome(96, 97).

Existent data on neuropsychological performance during migraine attacks is difficult to summarize due to a paucity of published studies, often based on small samples, having different designs and using distinct neuropsychological measures, often targeting specific cognitive domains (60, 96-100, 102, 103, 159, 218, 219). The profile of cognitive impairment is inconsistent, varying from dysfunction documented in several cognitive domains (attention, processing speed, working memory, calculation, visuo-motor processing, visual and verbal memory)(96-100, 102, 103) to normal performance(159, 218, 219). In addition, there is lack of control for factors that influence cognitive performance in general, such as mood changes (96, 102, 103, 159, 218) concomitant drug treatments, substance abuse or the practice effect of repeated neuropsychological testing. Migraine has its own potential confounders that also need to be considered, such as the presence of aura (a cortical phenomenon that might influence visual processing and speed(103, 159)), photophobia (that might interfere

with tasks requiring prolonged staring at a computer screen) and the effects of pharmacological agents, either migraine treatments or migraine-triggering drugs.

Our study was designed to evaluate cognitive changes during naturally occurring untreated migraine attacks, compared to headache free status. We selected a comprehensive battery of cognitive and behavioral tests targeting different cognitive domains that have been identified as disturbed on at least one previous study, and we controlled for anxiety, depression, pharmacological effects, presence of migraine aura and for the practice effect bias.

SUBJECTS and METHODS

Population

Otherwise healthy, episodic migraine patients were recruited consecutively on a Headache Outpatient Clinic, both from first and from follow-up visits. Inclusion criteria were: a) age between 20 and 65 years; b) ≥ 4 years of formal education; c) diagnosis of episodic migraine according to ICDH-II(186); d) ≥ 1 attack/month of migraine without aura in the 3 months preceding inclusion; e) living/ working near or at the study center (allowing an evaluation within 60 minutes of an established migraine attack); e) written informed consent. Exclusion criteria included the co-existence of any other headache type, chronic migraine, medication overuse, exclusive or very frequent attacks of migraine with aura, history of alcohol or drug abuse, and any medical or psychiatric disorder requiring daily treatment. In order to minimize potential cognitive effects of pharmacological agents, the only allowed daily medications were oral contraceptives and migraine prophylactics. The study protocol was approved by the Hospital and Faculty of Medicine Ethics Committee . There was no financial compensation for the volunteers.

Study design

Study design consisted of a randomized, two-period crossover study requiring two evaluations of the same subject in two different conditions : condition 1, during an untreated spontaneous attack of migraine without aura (Migraine Attack - M); condition

2, during a headache-free period that was not treatment-induced (Baseline - B) with a minimum of 72 hours elapsed since the last attack. Evaluation order was randomized, half the patients having the first evaluation while headache-free (B→M), while the other half was first evaluated during the attack (M→B). A minimum interval of one month between evaluations was required. This design had the purpose to control for the practice effect and minimize the need to determine the expected magnitude of improvement in neuropsychological testing between such short-term repeated evaluations(225, 228) Assessments took place during working hours and within 24 hours of the onset of the attack. Attacks occurring at night or during weekends, attacks with aura and attacks treated with abortive medication in the previous 12 hours were not eligible. ICDH-II criteria(186) for migraine without aura and absence of aura in the previous 48 hours were re-checked immediately before cognitive assessment in the evaluation during an attack.

Subjects were excluded if they did not have an eligible attack within a two-year period after inclusion. At the end of a five years enrolment period, the authors decided to terminate the study despite the initial goal of enrolling 50 evaluable subjects had not been met.

Study protocol

Recruitment and inclusion of study subjects were performed by headache specialists, who verified study criteria and carried out a standard clinical evaluation, including previous medical history and physical examination. After informed consent was obtained, data was collected and included verification of the ICDH-II diagnosis, gender, age, education years, disease duration, attack frequency, duration and intensity, and use of prophylactic treatment and other current treatments. Migraine impact was evaluated with the HIT-6(140) and MS-QoL(229) questionnaires. Depressive symptoms and anxiety were quantified with the Zung Depression scale(230) and the State-Trait Anxiety Inventory (STAI)(231) as depression and anxiety are frequent comorbidities of migraine(232) and can influence neuropsychological performance(139). Attack evaluation included questions about current attack features

as well as about pain intensity, which was scored before testing with a 10-point visual analogue scale (VAS).

Neuropsychological testing was applied by licensed neuropsychologists following a pre-selected comprehensive neurobehavioral battery (98, 118) which included internationally recognized tests applied in clinical practice and validated for our population. Tests were applied using paper-and-pencil, and not computerized, based on three considerations: (1) the experience of our neuropsychologists in the written form of tests; (2) the need to avoid the visual discomfort of a screen display on a photophobic patient; and (3) the attempt to minimize the risk of non-compliance, given the predicted long (40 to 60 minutes) duration of the evaluation, by introducing an interaction with the examiner. Tests were chosen in order to cover the main cognitive domains, as depicted in table 1. Test descriptions, reliability and practice effects are available in Table 2.

Table 1 – Neuropsychological Battery

	Cognitive Domain	**Neuropsychological tests**
EXECUTIVE FUNCTIONS	Attention	-Trail Making test A and B - Stroop test - Symbol Search - Digit Span Forward - Verbal Fluency
	Processing speed	-Trail Making test A and B - Finger Tapping - Stroop test - Symbol Search
	Mental Flexibility	-Trail Making test B and B-A - Stroop color word test - Verbal Fluency
	Inhibitory control and Monitoring	- Verbal Fluency - Stroop color word
	Working Memory	-Trail Making test A and B - Digit Span Backwards
LONG TERM	Visual Memory	- Visual Reproduction
	Declarative Episodic Memory	- Logical Memory
	Verbal Memory and Learning	- California Verbal Learning Test

	Declarative Semantic Memory	- Famous Faces Test
PERCEPTION & MOTOR CONTROL	Spatial and Visual Perception	- Symbol Search - Famous Faces Test
	Visuo-motor processing	-Trail Making test A and B - Visual Reproduction
	Motor Function and Speed	-Finger Tapping
LANGUAGE	Naming	- Snodgrass naming test - Famous Faces Test
	Verbal Initiative and fluency	- Verbal Fluency
	Reading	- Stroop Reading

Table 2 - Test description, reliability and practice effects

Test designation and description	Reliability and Practice effects
FINGER TAPPING TEST (FTT)(233)	
The Finger Tapping test records the total number of taps obtained in 10 seconds, using the index finger of each hand alternately. Test score is calculated averaging the number of taps obtained in three trials of each hand.	Reliability coefficients of the FTT in healthy adults vary in different studies, from 0.71 to 0.94(234, 235); practice effect is small and fades after the first repetition(236).
TRAIL MAKING TEST (TMT)(237)	
The Trail Making Test consists of two parts; in part A subjects have to connect numbers in an ascending numerical order (from 1 to 25) that are randomly spread in a sheet of paper. In part B subjects have to connect numbers (from 1 to 13) and letters (from A to L) that are randomly spread in a sheet of paper, in alternating ascending numerical and alphabetical order. Errors are pointed out by the observer and must be corrected without interruption of the stopwatch. The test scores the time spent to correctly complete the task (in seconds) and the number of errors made. Subtracting the time of Trail A from the time of Trail B is a measure of mental flexibility, because it removes bias induced by attention, motor speed and visual processing.	Reliability coefficients are always lower for part A than for part B of the Trail Making test; part B has a reliability of 0.65 or higher(238) and presents negligible practice effects (236).

STROOP TEST(239)	
The Stroop test includes three tasks; the first is the Reading task, in which the individual has to read aloud the maximum number of color names (out of a list of 100). In the second task, Color Naming, the individual has to name the maximum number of colors out of a list of 100 Xs printed in different colors. In the last task, the Interference Test, a list of 100 written color names are printed in a color that does not correspond to the color print; the participant must name the color and ignore the written word. Scores of each task are the number of items read in a given time (45 seconds) and the number of errors made.	The Stroop test has good reliability (> 0.91) and presents small practice effect in the second repetition(236).
VERBAL FLUENCY (233)	
The verbal fluency tasks accesses the individuals' ability to retrieve specific information in one minute. The two subtests used were the Semantic Verbal Fluency, in which individuals have to generate semantic category exemplars (in this case, animals) and Phonemic Verbal Fluency, for generating words beginning with a target letter (in this case, the letter "P"). The score is the total number of items generated per category, excluding repetitions and errors.	The verbal fluency tests have good reliability ranging from 0.68 to 0.73(240) and modest (although significant) practice effects(241).
SYMBOL SEARCH (242)	
The Symbol Search is a test in which a row with five symbols is compared with two targets. Subjects have to decide if the targets are repeated in each row. The score is the total number of correct answers given in 120 seconds.	The Digit Span test is a subtest of the Wechsler Adult Intelligence Scale (WAIS) presenting good reliability (0.91)(243).
DIGIT SPAN (242)	
In the Digit Span test a serial of random sequential digits of progressive length is orally presented and the participant has to repeat it immediately after its presentation, in two subtests – forward (digits have to be repeated in the order they were presented) and backward (digits have to be repeated in backwards order of presentation). Each sub-test scores the highest length of digits that is correctly repeated (ranging from 2 to 8), final score is the average of both sub-test scores.	The Digit Span test is a subtest of the Wechsler Adult Intelligence Scale (WAIS) having negligible practice effects and test-retest reliability coefficients ranging from 0.66 to 0.89 in normal individuals, depending on interval length and subject ages(244).
VISUAL REPRODUCTION (245)	
In the Visual Memory test three geometric pictures of increasing complexity are presented and have to be reproduced with as many details as possible immediately (short-term) and after 20 minutes (long term). The test score is given by adding the number of correct details reproduced in each drawing.	The Visual Memory test is a subtest of the Wechsler Memory Scale (WMS) that presents test-retest stability coefficients over 0.85 in healthy subjects(245) and small practice effects(246).

LOGICAL MEMORY(245)	
In the Logical Memory test the participant has to repeated back two stories with as many details as possible immediately (short term) and after 20 minutes (long term). Each story is scored by adding up the number of ideas that are correctly retained and final score represents the average of both stories.	The Logical Memory test is a subtest of the Wechsler Memory Scale (WMS) in which there is a large practice effect and test-retest reliability coefficients of 0.62 and 0.68(246).
CALIFORNIA VERBAL LEARNING TEST (CLVT) (247)	
The California Verbal Learning Test consists in five presentations of a list of 16 stimuli (words of four semantic categories) and requesting the retrieval of these stimuli immediately and after an interference list of different stimuli both at short term and after a 20 minutes delay (long term). Several scores can be calculated by counting the number of stimuli that the individual is able to recall - the learning ability (the sum of the five repetition trials), short and long term (delayed) recall after interference, cued recall (obtained by providing the semantic categories) and recognition.	The CVLT has having small to medium practice effects and test-retest reliability coefficients for total trials range from 0.80 to 0.84 in normal adults(248).
SNODGRASS NAMING TEST (249)	
The Snodgrass & Vanderwart Naming Test has 260 pictures that are presenting for naming. We used only 8 pictures (train, pear, eye, bed, ax, peacock, heart and watering can) that were chosen randomly. The test scores the number of correct pictures named.	No data available
FAMOUS FACES TEST(250)	
The Famous Faces Test consists of 71 face photographs of famous individuals or personalities from different nationalities, time periods and professional groups that have to be named by the subject. This test is sensitive to cultural differences between societies so we used a version that has been developed and validated in our country. We used only 7 faces (chosen to be representative different time periods and professional groups). The test score is the number of personalities named correctly.	No data available
STAI SCALE (231)	
The State-Trait Anxiety Inventory (STAI) is a self-rating 40 questions scale that quantifies anxiety levels in two contexts – state reports to anxiety related to an event or moment (20 questions), trait reports on usual personal level of anxiety (20 questions). Each question is scored from 1 to 4, higher scores representing higher anxiety levels. The scale score is obtained by summing the scores of each item.	
ZUNG DEPRESSION SCALE(251)	
The Zung Depression Scale is a self-rating 20 questions scale that quantifies depressive symptoms; each question is scored from 1 to 4, higher scores representing higher depressive symptoms.	

Statistical Analysis

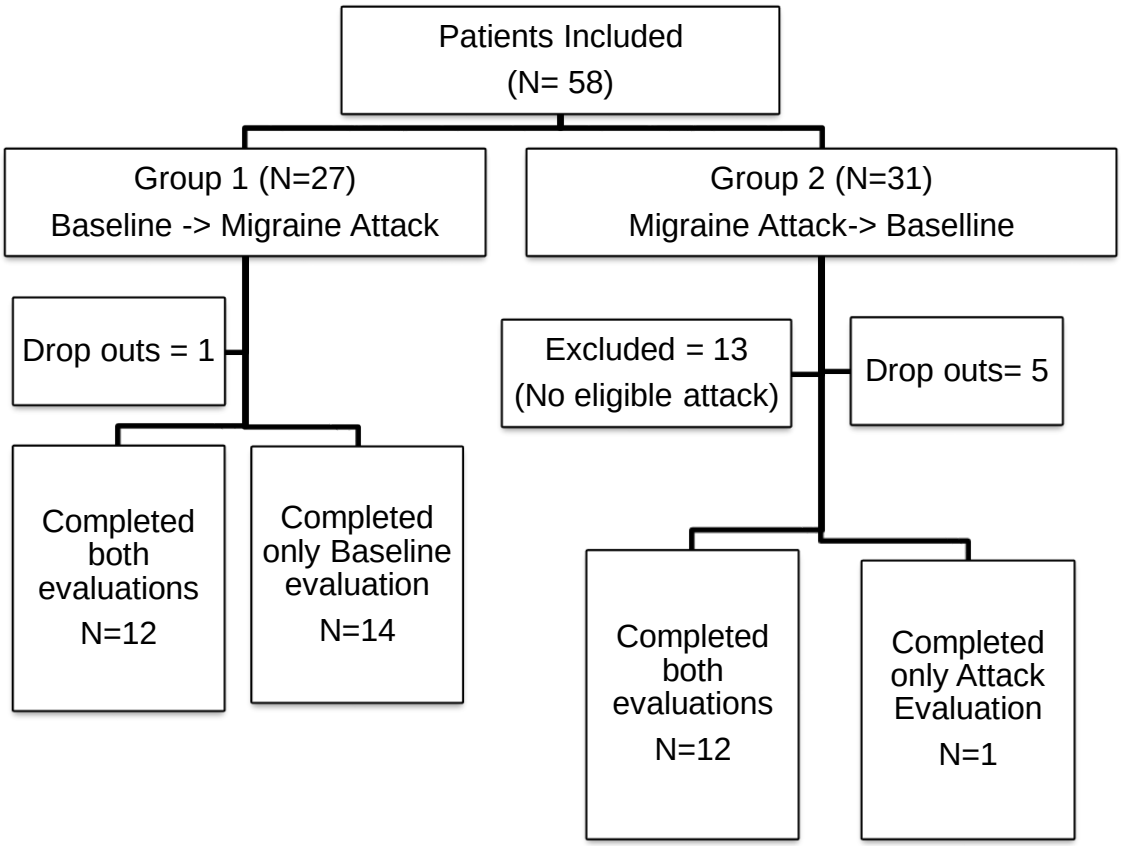
Statistical analysis used SPSS v20. Frequencies and means ± standard deviations were used for descriptive statistics. Two-sample t-tests were used to compare baseline patient variables between randomization groups. The effect of the exposure to a migraine attack on the test scores, controlling for a learning effect, was tested with two-sample Student's t-tests of the difference between groups in the change in test scores from the first to the second evaluation (252). A learning effect was tested with standard t-tests of the difference between groups in the change in test scores from the evaluation during an attack to the baseline evaluation. An exposure-by-period interaction was tested with standard t-tests of the difference between groups in the sum of the two evaluations of each subject. Data was tested for normality with the Shapiro-Wilk test and the test scores with non-normal distribution were analyzed with the non-parametric Wilcoxon-Mann-Whitney ranksum test, instead of t-tests. The Hochberg step-up procedure(253) was adopted to account for multiple testing and to provide strong control of the type I error at the 5% significance level. Reported p-values are adjusted for multiplicity using the Bonferroni correction(206). For each test showing a significant difference between the two evaluations we used multiple linear regression to evaluate the effect of the following variables on the identified difference: gender, age, literacy, time between evaluations, anxiety, pain intensity and duration of the attack. The power of this study is 70% to detect a difference in test scores between evaluations greater than 0.8 standard deviations, at the two-sided 0.05 significance level.

RESULTS

1- Population and Study Flow

Fifty-eight subjects were randomized, 27 to have their first evaluation while headache-free (B→M) and 31 to have the first evaluation during a Migraine attack (M→B). There were 34 non-completers (6 withdrawn from the study, 13 did not have an eligible attack within 2 years and 15 only performed one of the evaluations). Twenty-four patients (12 from each group) were able to complete the study (Figure1).

Figure 1 – Study flow and sample



The study population consists of 24 patients, all right-handed but one. Table 3 shows the baseline characteristics of patients. Four (17%) had migraine with and without aura (3 visual, 1 visual and somatosensory). The sample had an average of 38.0±11.6 years of age (range 21 to 63), 19.3±12.1 years of education (range 4 to 22) and average disease duration of 19.3±12.1 years (range 3 to 57). Average Zung score was 48.7±8.0 (range 35 to 79) and 8 subjects had scores corresponding to mild depression but none was severely depressed.

Table 3 - Patient characteristics

Variable	**Group B→M**		**Group M→B**		**Total**		**p**
	n=12		n=12		n=24		
Age (av, sd)	39.0	11.5	36.9	12.1	38.0	11.6	0.67

Females (n, %)	11	9.7	12	100.0	23	95.8	0.99
Migraine with aura	2	16.7	2	16.7	4	16.7	0.99
Education years (av, sd)	13.7	5.8	12.2	5.3	12.9	5.5	0.51
Disease duration years (av, sd)	21.8	13.5	16.6	10.2	19.3	12.1	0.31
Zung score (av, sd)	48.3	4.4	49.1	10.7	48.7	8.0	0.82
Positive Zung score (n, %)	4	33.3	4	33.3	8	33.3	0.99
1-4 attacks monthly (n, %)	5	41.7	6	50.0	11	45.8	0.99
Attack duration <24 hrs (n, %)	4	33.3	6	50.0	10	41.7	0.68
Moderate intensity (n, %)	5	41.7	7	58.3	12	50.0	0.68
Drug prophylaxis (n, %)	3	25.0	4	33.3	7	29.2	0.99
HIT-6 score (av, sd)	64.5	4.4	62.1	9.4	63.3	7.3	0.43
MSQoL score (av, sd)	76.4	14.1	74.8	14.6	75.6	14.1	0.79
Days between evaluations (av, sd)	287	141	124	147	206	164	0.012

On inclusion, the majority of patients (45.8%) had 1-4 attacks monthly, most (42%) lasting 4 to 24 hours and of moderate to severe intensity (100%). Seven participants (29%) were receiving migraine prophylactics (2 propanolol, 2 propanolol and amytriptiline, 2 amytriptiline and 1 topiramate and amytriptiline). Migraine impact was moderate to high, with an average HIT-6 score of 63.3±7.3 (range 45 to 76) and an MSQoL score of 75.6 ± 14.1 (range 43 to 95).

Time between evaluations was on average 206±164 days (about 6 months, range 26 to 568 days). Patients in group (B→M) had a higher interval between evaluations (287±142 days, ≈9 months) than group (M→B) (125±147 days, ≈4 months, p=0.012); no other differences were documented between the groups (table 3).

2- Attack and Baseline cognitive performance analysis

At the time of the studied attack, patients had experienced an average of 3.1±2.5 (range 0 to 10) attacks in the previous month, lasting an average of 33.2±29.6 hours (range 30 minutes to 96 hours). Ninety two percent of the previous attacks were of moderate to severe intensity.

During this attack, 2 patients (8%) experienced vomiting, 15 (62.5%) photophobia and mean VAS pain intensity was 5.7±1.6 (range 3 to 9.5). Average duration of symptoms at the time of the evaluation was 8.2±8 hours (range 30 min to 28h, median 5h45 minutes).

Average uncorrected raw test scores are shown in table 4. Two measures were removed from the analysis: errors in Trail Making Test (TMT) were too few to be compared and the Snodgrass naming test showed a ceiling effect in all evaluations.

Table 4 –Average uncorrected raw scores of neuropsychological tests in each evaluations and mean difference of raw scores between evaluations (Baseline-Migraine)

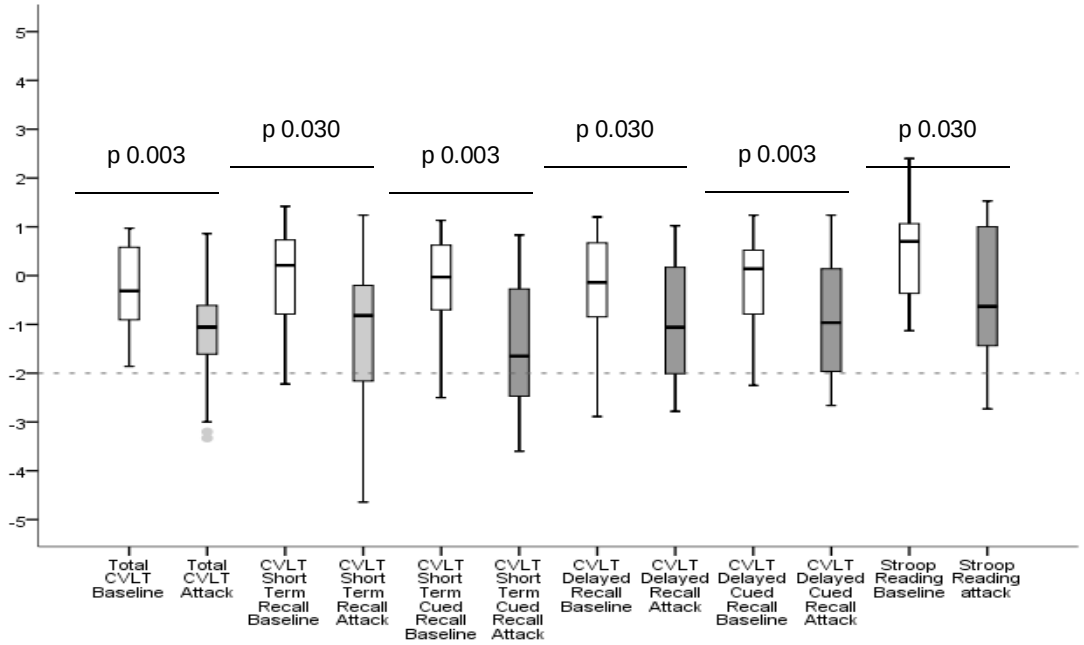
	Baseline mean ± sd	Attack mean ± sd	Mean Difference (B-M) mean ± SEM	p	p (order effect)	p (inter-action)
Executive function tests and measures						
Finger tapping (dominant hand) †	45.9 ± 8.4	41.8 ± 10.0	4.08 ± 1.46	0.009	0.37	0.62
Finger tapping (non-dominant hand)	40.3 ± 7.6	37.8 ± 8.4	2.47 ± 1.52	0.09	0.10	0.21
Digit Span Forward	7.0 ± 2.6	6.1 ± 2.6	0.88 ± 0.38	0.03	0.59	0.84
Digit Span Backwards	5.9 ± 1.7	5.3 ± 2.0	0.58 ± 0.47	0.24	0.86	0.50
Digit Span Total †	12.8 ± 3.9	11.4 ± 3.7	1.42 ± 0.63	0.03	0.81	0.64
Stroop words (reading) †	90.6 ± 17.1	77.6 ± 21.0	13.0 ± 3.55	0.0006**	0.02	0.41
Stroop colors	67.1 ± 13.7	58.6 ± 13.9	8.45 ± 2.55	0.003	0.18	0.03
Stroop Interference	38.8 ± 10.3	36.8 ± 12.7	2.04 ± 2.08	0.32	0.09	0.35
Fluency Animals	19.3 ± 4.5	18.3 ± 6.6	1.00 ± 0.87	0.26	0.35	0.50
Fluency Letter P	11.7 ± 4.9	10.0 ± 5.1	1.71 ± 0.61	0.01	0.74	0.21
Trail A Time	38.3 ± 14.1	45.1 ± 15.5	-6.75 ± 2.56	0.01	0.26	0.60
Trail B Time †	91.1 ± 54.0	102.8 ± 56.8	-11.8 ± 8.68	0.08	0.09	0.82
Trail difference (B-A) †	52.8 ± 46.0	57.8 ± 47.1	-5.00 ± 8.34	0.44	0.51	0.84
Trail A errors †	0.0 ± 0.2	0.1 ± 0.3	-0.04 ± 0.07	0.58	0.58	0.55
Trail B errors	0.2 ± 0.4	0.5 ± 0.8	-0.29 ± 0.14	0.04	0.14	0.18
Symbol Search	31.8 ± 10.9	29.6 ± 10.6	2.17 ± 1.12	0.06	0.10	0.68
Other tests (memory, language)						
Naming †	7.8 ± 0.5	7.7 ± 0.5	0.04 ± 0.11	0.96	0.31	0.91
CVLT first immediate recall	7.8 ± 2.4	6.9 ± 2.2	0.88 ± 0.42	0.06	0.92	0.11

CVLT total learning	60.2 ± 9.8	52.5 ± 12.1	7.63 ± 1.83	0.0003*	0.91	0.20
CVLT fifth recall	14.1 ± 2.2	12.5 ± 3.2	1.63 ± 0.60	0.014	0.46	0.32
CVLT short term free recall	13.0 ± 2.6	11.2 ± 2.8	1.87 ± 0.48	0.0004**	0.07	0.97
CVLT short term cued recall	13.5 ± 2.6	11.6 ± 2.8	1.88 ± 0.45	0.0003*	0.12	0.84
CVLT delayed free recall	13.0 ± 2.6	11.6 ± 2.9	1.38 ± 0.38	0.0015**	0.45	0.58
CVLT cued delayed recall	13.7 ± 2.4	12.0 ± 2.8	1.63 ± 0.34	0.0001*	0.28	0.72
WMS-III Logical Memory – immediate recall	15.0 ± 5.4	12.9 ± 4.9	2.10 ± 0.90	0.36	0.83	0.96
WMS-III Logical Memory – delayed recall	14.7 ± 5.5	11.8 ± 4.9	2.90 ± 0.95	0.008	0.76	0.72
WMS-III immediate visual memory	11.9 ± 2.9	12.3 ± 2.7	-0.46 ± 0.53	0.41	0.82	0.50
WMS-III delayed visual memory	11.0 ± 3.1	11.5 ± 3.1	-0.46 ± 0.52	0.38	0.18	0.60
Famous faces test	5.9 ± 1.5	5.3 ± 1.5	0.58 ± 0.28	0.05	0.57	0.54
Other measures						
STAI – state	32.2 ± 7.7	45.5 ± 11.7	-13.3 ± 2.64	0.0001*	0.23	0.61
STAI – Trace	38.9 ± 6.7	38.6 ± 6.7	0.3 ± 4.3	0.81	0.22	0.17

Legend: sd: standard deviation; SEM: standard error of the mean; †: Wilcoxon-Mann-Whitney ranksum test, otherwise Student's t-test; *: $p<0.01$ and **: $p<0.05$ after adjustment for multiple comparisons

Significant differences were observed in Stroop word reading (p=0.013), California Verbal Learning Test (CVLT) total learning (p=0.01), CVLT short term recall with (p=0.01) and without (p=0.013) semantic help, and delayed recall with (p=0.003) and without (p=0.05) semantic help (Figure 2). The anxiety state was higher during the attack (p=0.003) but trace anxiety showed no difference. There was evidence for a learning effect in Stroop word reading (p=0.009) but no evidence that the learning effect was different between groups (p for interaction=0.28).

Figure 2 – Differences in test performance of Baseline versus during a Migraine Attack



Legend: X axis: Neuropsychological Tests ; Y Axis: Z Scores; White boxes : Baseline Evaluations; Dark boxes: Attack evaluations

The effect of the clinical (independent) variables (gender, age, literacy, time interval between evaluations, anxiety, pain intensity and duration of the attack) on the differences found between the two evaluations of the Stroop reading, CVLT total learning, CVLT short term free and cued recall, CVLT delayed free and cued recall were analyzed with multiple linear regression. Pain intensity during the attack was found to influence in CVLT short term free recall (p=0.008) but no other variable influenced the differences found in the tests (table 5).

Table – Multiple linear regression analysis to evaluate the effect of the clinical (independent) variables on the differences between evaluations identified in each test (dependent variables).

	DEPENDENT VARIABLES					
INDEPENDENT VARIABLES	Stroop reading task	CVLT total learning	CVLT short term free recall	CVLT short term cued recall	CVLT delayed free recall	CVLT delayed cued recall
Gender	B 12.736, p 0.554	B -14.614 p 0.219	B -5.549, p 0.020	B -2.940, p 0.303	B -1.623, p 0.548	B -0.520, p 0.835

Age	B -0.604, p 0.258	B 0.096, p 0.734	B -0.096, p 0.084	B -0.104, p 0.144	B -0.028, p 0.669	B -0.009, p 0.879
Literacy	B 0.056, p 0.955	B 0.090, p 0.867	B -0.136, p 0.188	B -0.250, p 0.071	B -0.070, p 0.579	B -0.022, p 0.851
Stay State (attack)	B 0.531, p 0.144	B -1.185, p 0.334	B -0.013, p 0.719	B 0.018, p 0.689	B 0.015, p 0.733	B 0.035, p 0.391
Attack duration	B -0.677, p 0.228	B 0.030, p 0.919	B -0.072, p 0.205	B -0.046, p 0.526	B -0.061, p 0.377	B 0.010, p 0.878
Pain intensity in the attack	B 3.368, p 0.209	B 3.388, p 0.028	B 0.688, p 0.008*	B 0.326, p 0.347	B 0.209, p 0.525	B 0.097, p 0.750
Time between evaluations	B 0.041, p 0.110	B -0.015, p 0.267	B -0.004, p 0.128	B 0.000, p 0.915	B -0.001, p 0.814	B -0.002, p 0.513

Legend: B = Unstandardized beta coefficient; p = significance level; * significant at p< 0.010; CVLT – California Verbal Learning Test

DISCUSSION

This study showed that migraine attacks are associated to a nominal performance decline in the majority of neuropsychological tests in relation to headache-free periods. The only exception were measures with a ceiling effect and those, such as the visual reproduction test, that are sensitive to practice(254).The decreased test performance during migraine was significant in two tests – the word reading task of the Stroop test (measuring processing speed and reading) and the CVLT (measuring learning and memory). The observed decline in performance was unrelated to the order of and time between evaluations, anxiety state and attack duration; only pain intensity was found to influence the short term free recall of the CVLT, a measure related to the retrieval process(255).

This cognitive impairment seems related to the attack itself, giving objective support to patient's subjective complaints(98, 118, 159) and corroborating previous studies that have demonstrated reversible dysfunction in processing speed, working memory, visual-spatial processing, alertness/ fatigue (96, 98, 102, 105, 159), immediate and sustained attention, verbal learning(100, 105) and inhibition(105). The predominant involvement of processing speed, learning and memory could suggest a preferential dysfunction of the pre-frontal and temporal cortices and/or frontal

subcortical white matter during migraine attacks, an observation supported by functional imaging findings during migraine attacks showing changes in the cingulated and pre-frontal cortex(153) insula and the temporal lobe(152) .

The observed decline in word reading speed of the Stroop test might be related to an impaired automatic process of attending to the lexical features of words or reduced processing speed. Visual abilities, such as low contrast sensitivity in older individuals has also been linked to slower performance on word reading(238) yet visual factors are an unlikely explanation of these finding in our sample of young otherwise healthy migraine without aura subjects. The two other subtests of the Stroop test did not show a significant decline in performance. This suggests that conscious process of color naming, which involves the discrimination and retrieval of names, attention and verbal response was maintained, as was selective attention and the ability of suppress an automatic response which the interference task and seems to be consistently correlated to activation of the anterior cingulated cortex(256). Additional support of the functional integrity of pre-frontal cortical systems was the adequate performance on the remaining tests directed to executive functions such as set shifting, divided attention, mental flexibility, processing speed and verbal working memory.

Decline in episodic memory tasks was consistent across the retrieval measures of the CVLT test, reflecting a verbal learning and retrieval impairment, tasks supported by a large network involving the hippocampus, medial temporal lobe and prefrontal (dorsolateral) cortex(257, 258) and connectivity between the thalamus and the putamen and striatum (259). The additional memory tests performed, that targeted famous faces naming and recognition (semantic memory), logical and visual memory were not selectively impaired, which may relate to lower relative sensitivity of these tests (260)in which a higher level of contextual information is presented. Another possible explanation is a higher resistance of the anterior and dorsal lateral prefrontal cortices function during migraine, as those are specifically involved in the context-related retrieval process(261).

Our data therefore favors the involvement of temporal(152) or sub-cortical nuclei during the migraine attack, over pre-frontal or the cingulate cortices(153).

The mechanism by which cognitive impairment occurs during migraine without aura attacks is speculative. It may relate to a cortical spreading depression-like

phenomena occurring during migraine without aura, shown to decrease cerebral blood flow (CBF) in the occipital, temporal and parietal lobes.

Cognitive dysfunction in migraine can also be secondary to influences of sub-cortical stuctures, namely the raphe nuclei and its cortical serotoninergic projections (ex. orbitofrontal cortex, precentral gyrus, temporal pole, insula and somatosensory area) . An alternative subcortical candidate is the thalamus, that is activated during attacks in humans(153) and whose activity was shown to control cortical states and influence perception, learning and cognition in animal studies(262).

An important issue that is not answered by this study design is whether these findings are specific to migraine or could be simply induced by the cognitive processes related to the pain experience. A wide range of neuropsychological and imaging changes have been described in chronic pain populations that support an impairment in attention, executive and general cognitive function, as a consequence of long-term pain-related neurochemical and neuroplastic brain changes(89). This data cannot be inferred to episodic pain, despite there being some evidence for interictal brain changes in migraine (263). Studies on the effects of acute pain in healthy volunteers have consistently documented hemodynamic responses in the primary somatosensory (SI) cortex (a pain processing area), bilateral insula and second somatoensory (SII) cortices (regions involved in somatosensory integration that is influenced by attention), bilateral thalamus and brainstem (discriminative and arousal pain responses and descending pain modulation) but also other higher cognitive relay areas such as the anterior cingulated cortex (involved in the cognitive-attentional response to pain and anticipation of pain) and the dorso-lateral prefrontal (DLPF) and posterior parietal cortices (related to cognitive aspects of pain processing)(264). Involvement of these areas during pain processing could be the reason for decline in certain neuropsychological tests, in particular in tasks requiring attention (265), although this is not consistent with the cognitive profile shown in this study.

A recent fMRI study on migraine was able to demonstrate enhanced functional connectivity of the anterior temporal pole with pain related cortical structures involved in acute pain processing, which suggests that the pain-processing mechanism of the migraine attack may not be entirely identical to experimental acute pain. In particular, this study was able to demonstrate hyperexcitability of the anterior temporal pole in the

interictal phase of migraine that increased during the attack(152), giving support to our observation of pain intensity influencing some measures of the CVLT.

Another argument against the effect of pain by itself is the fact that cognitive subjective symptoms are reported during the prodrome of the migraine attack, before pain arises(121).

The main strengths of this study are its design that dealt with most bias and confounders: the migraine population that was free of psychiatric co-morbidities and medication overuse, the use of an extensive neuropsychological battery covering the main cognitive domains and the control for multiple testing in the analysis. Studies with neuropsychological evaluation of migraine patients during attacks imply motivating patients to come into office during an untreated attack and keeping them cooperative during a one-hour testing. For that reason, as well as because of photophobia, it was important that the tests were paper-and-pencil instead of computerized (which may be more sensitive to reaction times). Interaction with the examiner was used to improve task engagement and to ensure adequate compliance levels throughout the evaluation. However, this made blinding impossible and did not allow the use of more accurate tests to measure reaction speed.

The most important limitation of this study was the difficulty to assess patients during the attack: 18 subjects were excluded or dropped-out because of not being able to be evaluated during an attack; only 12(46%) of the patients first evaluated at baseline managed to return during the attack, while only one patient first evaluated during an attack did not return for the second, baseline evaluation. The time lapse between evaluations in both groups was also quite different; the delay of the group starting with the attack evaluation almost doubled the delay of the other group. These facts had implications in the interpretation of the results and an impact in final sample size which, although in line with the sample sizes from previous studies (96, 98, 100, 103, 159, 218, 219), was insufficient to ensure adequate statistical power to attain significant statistical differences in some tests. Our difficulty in ensuring the actual participation of subjects during the attack was perhaps influenced by the lack of financial compensation of participants, as evaluations were only possible during working hours. We also acknowledge that some cognitive aspects could have been better detailed. In particular, a more comprehensive executive testing would be preferable to study frontal lobe

dysfunction and the inclusion of measures of crystallized intelligence would help in identifying the cognitive profile of dysfunction, such as a dissociation decline between fluid and crystallized intelligence, with potential implications in actual cognitive performance Poor effort could have influenced neuropsychological scores obtained in this study, as we have not included a measure of effort in our battery. Finally, as stated earlier, the amplitude of estimated practice effect was not taken into consideration since it was minimized by the design of the study that allowed all participants to gain practice with the tests at first exposure.

Our study supports existing literature that reports neuropsychological and neurophysiological evidence of reversible brain dysfunction occurring during the migraine without aura attack, that probably underlies migraine-related cognitive impairment(266). These findings are crucial in supporting patients' claims of attack-related cognitive impairment and have clinical implications in relation to working and learning abilities during attacks and also on the evaluation of response to acute migraine treatment. In the research setting, it may help in the enlightening of the nature of brain dysfunction in migraine. More studies are needed to determine if the attack-related cognitive impairment is specific of migraine pathopshysiology or is simply related to acute pain processing by the brain.

Sequential evaluation of migraine patients and controls using a short neuropsychological battery.

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Sequential evaluation of migraine patients and controls using a short battery of cognitive assessment.

Acta Neurologica Scandinavica 2015 *[in press]*

ABSTRACT

Background: Evidence of attack-related cognitive dysfunction in migraine is growing. Controversy exists on whether cognitive dysfunction, mainly executive, may persist between attacks. Measuring the impact of cognitive function is gaining importance in clinical and research settings in Migraine.

Objective: To compare the performance of interictal migraine patients to controls in an assembled neuropsychological battery focused on executive functions and to study the practice effect of its repeated applications.

Method: Assembly of the battery that was then applied twice within 6 weeks to interictal migraineurs and matched healthy controls.

Results: Migraine patients (n=24) and controls (n=24) had similar performance in both applications of the battery. There was a slight practice effect between the first and second evaluation, significant in Stroop Interference test (p=0.002, multiplicity corrected); a meaningful score change was determined for each raw test scores.

Conclusions: Interictal migraineurs and controls performance is identical in a brief cognitive battery focused on executive functions. Repeated applications produced a practice effect that was quantified. This short and practical battery may become a tool to measure the cognitive dysfunction of migraine attacks.

INTRODUCTION

Cognitive subjective symptoms are often reported during migraine attacks (95, 118, 133, 136, 156), contribute to patient disability (95) and may persist after successful pain control(158). Dysexecutive (attention, concentration, planning, judgment, initiative, speed) and language symptoms are the most frequent spontaneous attack-related complaints (98, 118). Supporting these subjective complaints, some evidence of reversible attack-related cognitive dysfunction exists(108), in processing speed(109), working memory, visual-spatial processing, alertness/fatigue(60, 96, 98, 102, 159), attention and verbal memory and learning (100, 109).

Some studies even documented the persistence of these symptoms at long term, in subgroups of patients with severe attacks, with aura (59) or in children (267). Persisting migraine at old age also seems to influence sustained attention and processing speed (268). Large studies performed in community-based cohorts (183-185, 269, 270), in twins (271), and longitudinal studies (270, 272) were nevertheless unable to identify long-term changes in cognitive profiles of migraineurs.

Measuring migraine related cognitive dysfunction is increasingly crucial in determining migraine impact and migraine related disability. We are unaware of the existence of any objective measure of migraine-related cognitive impairment. The major problem of producing a measurement of neuropsychological dysfunction related to migraine is to determine if it can be useful in both migraine status – during attacks and while pain free. Assuming that patients may have different performances in different migraine status, the second problem will be that of the bias of the practice or learning effect of repeated test applications. Additionally, such a measurement should be practical, to be useful both in clinical and research settings. As so, it needs to be brief, reliable, provide different cognitive measures and be easily applicable with scarce resources. To be promptly available it must include valid routine or well-known tests that must evaluate the domains most likely to be affected, both during attacks and while pain free – executive functions and language.

In this study our aim was to (1) assemble a short battery using routine brief and reliable neuropsychological tests focused on executive functions and verbal skills; (2) to compare the interictal performance of migraine patients to matched healthy controls; (3) to study its practice effects over a short test-retest interval and (4) to identify the

predictable score intervals for which a change in test scores in repeated applications could be judged clinically meaningful.

SUBJECTS and METHODS

The study protocol was approved by the Hospital da Luz Ethics Committee. This is a prospective longitudinal study with two evaluations with a minimal interval of one month in-between, studying migraine patients while headache-free and healthy matched controls. Volunteers were recruited among the hospital staff by internal mail and intranet advertisement. Inclusion criteria were: a) age between 20 and 45 years; b) at least nine years of education; c) cases had either an history of episodic migraine without aura, as defined by the ICDH-III(7) , and controls were individuals without headaches (less than three headache episodes per year, none fulfilling the ICDH-III criteria for migraine or probable migraine); d) written informed consent.

Exclusion criteria were a) presence of any other headache type including migraine with aura, chronic migraine with or without medication overuse or chronic or frequent episodic tension-type headache; b) history of past or current alcohol or drug dependence or abuse; c) history of past severe medical, neurologic or psychiatric disorder; d) current use of any psychoactive medication including migraine prophylactics; e) pregnancy or lactation.

Three females were included for each male. Recruitment was stratified by three age groups (21 to 29, 30 to 37 and 38 to 45 years). Within each age group, one sex-matched control was included for each migraine case. Recruitment, inclusion and evaluation were made by one of the authors (RGG), who verified inclusion and exclusion criteria and performed standard clinical evaluation, including medical and neurological history and examination. Volunteers with migraine were only evaluated if they had had a free interval of at least 48h since the last attack. After informed consent, protocol data was collected, including clinical and ICDH-III diagnosis for volunteers with migraine, gender, age, literacy, age at symptom onset, current frequency and duration of attacks, and use of prophylactic treatment and/or other current treatments. The presence of depressive symptoms was quantified with the Beck Depression Inventory (273, 274).

Neuropsychological Battery – Development and description

Tests were included in this battery according to 3 criteria, (1) Tests should be used in routine clinical practice and recognized as valid measures of the target functions, (2) should be brief and easy to apply, with minimal resources and without the need for computerized support and (3) should aim to evaluate the cognitive domains corresponding to complaints and to functions reported as impaired during migraine attacks. A panel of headache specialists and expert neuropsychologists selected the relevant tests based on the aforementioned criteria, as well as on their personal experience with the tests and on a literature review. The panel also evaluated the duration of each test, the complexity needed for its application and the potential of the test to have a marked practice or ceiling effects, as the target population is young and literate. The result was a battery with a total application time of around 6 minutes, composed by the following tests: Finger Tapping(233) (motor speed), Trail Making Test(237) (attention, shift), Stroop Test (interference task)(239) (processing speed , inhibitory control), Reverse Digit Span(245) (verbal working memory), phonemic (Letter "p") verbal fluency(275) (verbal initiative, monitoring and semantic memory) and naming of 5 compound nouns from the Aachen Aphasia Test(276) (noun retrieval).

Measures and Scores

Finger tapping measures motor speed, and its results were averaged for the three 10 second trials of each hand(233). Trail Making test produces three measures, time in seconds to complete part A (attention and processing speed), part B (divided attention) and difference B-A(237). Stroop interference measures inhibitory control and was scored as the number of colors named in a minute. Digit span backwards is a measure of working memory and is scored by the longest sequence of digits correctly repeated. The Aachen Aphasia Test includes several naming tasks so we selected the 5 items that showed higher difficulty with normal young controls. The answers were scored progressively if correct (score of 3) or if having some (score 2) or little (score 1) resemblance with the target noun(276). Phonemic verbal fluency evaluates verbal initiative and monitoring and produced four scores, the total number of words

generated, number of correct words generated (excluding errors and repetitions), number and size of clusters (that represented groups of 2 or more words with semantic or phonemic similarities - semantic if belonging to the same semantic category or phonemic, if having the same initial sound or termination) and switching (that represents number of transitions between clusters, including single words, errors and repetitions)(277). Analysis and classification of the phonemic verbal fluency task was done by two independent observers and cases of conflicting classification were resolved by consensus.

Statistical Analysis

Statistical analysis used SPSS v20. Frequencies and central tendency measures were used in descriptive statistics. The Kolmogorov-Smirnov test was used for normality testing. Two-sample t-tests were used to compare baseline patient variables. Comparison of means between the two study evaluations was performed with the paired t-test.

The Holm-Bonferroni step down procedure(278) was adopted to account for multiple testing and to provide strong control of the type I error at the two-sided 5% significance level. Reported p-values are adjusted for multiplicity using the Bonferroni correction(206). For each test with a significant difference between the two evaluations we used multiple linear regression to evaluate the effect of several variables on the identified difference.

For test-retest reliability we computed the Intraclass Correlation Coefficient between baseline and follow up scores for each test. The practice, or learning, effect of each test was estimated by averaging the difference of the raw test scores between the second and the first application of the test in each subject (Individual improvement = Score 2nd evaluation – Score 1st Evaluation). The standard error of the difference was determined from the standard error of measurement in each test and the 90% confidence intervals for the expected retest scores were determined (279). The 90% confidence interval of the averaged practice effect was used to determine the expected improvement interval for each test(279).

RESULTS

1- Population

The study population consisted of 48 volunteers (12 males), four left-handed, of whom 24 had migraine without aura. The average age (± standard deviation) was 33.3 ± 7.2 years (range 22 to 45 years) with 13.8± 3.1 years of literacy (range 9 to 20 years). The average score on the Beck scale in the first evaluation was 6.1 ± 7.1 (range 0 to 32). Although some subjects had scores in the range of depression, none of the volunteers were currently being treated with antidepressants, nor had clinical diagnosis of depression. Current non-complicated medical illnesses included asthma (2), hypertension (1), smoking habits (11), glaucoma (1), hypercolestrolemia (1), and diabetes (1). In the total study population, 22 (56%) individuals were currently on daily medication, including 18 (82%) on oral contraception, 2 on asthma treatment, 1 with glaucoma topic treatment and 1 with statin treatment.

The average time between evaluations was 45 ± 13.6 days (range 35 to 108 days). In the migraine group, average disease duration was 17.5± 5.9 years (range 10 to 33 years). Upon inclusion, average attack frequency was 2.5 ± 2.0 per month (range from less than 1 to 8) and average attack duration was 22.7 ± 24.5 hours, ranging from 1 to 96 hours. No patient was currently on migraine prophylactics.

Migraineurs and controls were successfully matched in demographic characteristics. Groups were similar regarding and dominance, literacy, concomitant diseases, current medication use and average Beck score.

2.3 - Cognitive performance analysis – Difference between evaluations

Table 1 shows the results of the neuropsychological evaluation with the data presented as raw scores. The only test in which a statistically significant difference was found was the Stroop interference test, having an average increase of 4.9 items (p=0.002) and an average decrease of 0.4 errors (p=0.025) from the first to the second evaluation. In fluency tasks there was a slight increase of size in phonemic clusters (p=0.048).

Table 1 – Results of neuropsychological tests in both evaluations and Mean difference of raw scores (second-first) between evaluations

	1st Evaluation	**2nd Evaluation**	**Mean Difference (2nd-1st)**
Finger tapping (dominant hand)	55.9 ± 8.1	57.5 ± 6.5	1.6 ± 5.4
Finger tapping (non-dominant hand)	51.1 ± 6.8	51.1 ± 6.1	0.0 ± 4.2
Trail A Time	28.7 ± 8.1	26.3 ± 7.6	-2.4 ± 6.3
Trail B Time	81.9 ± 32.5	71.4 ± 27.5	-10.5 ± 28.1
Trail difference (B-A)	53.1 ± 30.1	45.1 ± 25.8	-8.0 ± 28.6
Trail A errors	0.2 ± 0.4	0.1 ± 0.3	-0.1 ± 0.5
Trail B errors	0.8 ± 1.2	0.7 ± 1.0	-0.1 ± 1.0
Digit Span Backwards	4.1 ± 0.9	4.2 ± 1.0	0.1 ± 1.0
Stroop Interference*	44.3 ± 8.4	49.2 ± 9.0	4.8 ± 3.8
Stroop Errors†	0.8 ± 0.8	0.4 ± 0.6	-0.4 ± 0.8
Naming – Total	13.6 ± 3.0	14.1 ± 0.8	0.4 ± 2.9
Fluency (letter P, total)	12.1 ± 4.0	13.6 ± 4.3	1.4 ± 3.6
Fluency (number of phonemic clusters)	2.5 ± 1.5	3.3 ± 1.3	0.8 ± 1.8
Fluency (size of phonemic clusters)‡	6.0 ± 3.8	8.2 ± 3.4	2.2 ± 4.7
Fluency (switching of phonemic clusters)	8.1 ± 3.6	8.4 ± 3.4	0.3 ± 4.1
Fluency (number of semantic clusters)	1.7 ± 1.0	2.2 ± 1.4	0.5 ± 1.4
Fluency (size of semantic clusters)	4.1 ± 2.7	5.2 ± 3.4	1.1 ± 3.6
Fluency (switching of semantic clusters)	9.1 ± 3.3	9.5 ± 4.7	0.4 ± 3.5

Legend: Paired T-Test was used to compare means; significant differences are: (*) p=0.002, (multiplicity-adjusted p-value); (†) p=0.025, (multiplicity-adjusted p-value); (‡) p=0.048, (multiplicity-adjusted p-value)

Effects of gender, age, literacy, time lapse between evaluations, Beck Depression score and migraine in Stroop performance were analyzed with linear regression and no associations were identified.

2.2 - Cognitive performance analysis – Migraine patients versus controls

No statistically significant difference was shown in any neuropsychological test performance between individuals with migraine and controls, both in the first and second evaluations, as well as in mean differences in test performance between evaluations (Table 2). Improved performance in the Stroop interference test was not documented in any of the groups (migraine and controls) individually.

Table 2 – Results of neuropsychological tests in both evaluations between migraine patients and controls

	1st Evaluation		**2nd Evaluation**	
	Migraine	**Controls**	**Migraine**	**Controls**
Finger tapping (dominant hand)	55.3 ± 6.8	56.4 ± 9.3	57.0 ± 5.7	57.9 ± 7.4
Finger tapping (non-dominant hand)	49.9 ± 5.7	52.3 ± 7.6	50.4 ± 4.7	51.9 ± 7.2
Trail A Time	28.6 ± 8.4	28.9 ± 7.9	26.8 ± 6.4	25.9 ± 8.8
Trail B Time	76.3 ± 24.2	87.4 ± 38.9	69.3 ± 21.6	73.5 ± 32.8
Trail difference (B-A)	47.7 ± 20.1	58.6 ± 37.2	42.5 ± 20.1	47.6 ± 30.7
Trail A errors	0.3 ± 0.5	0.1 ± 0.3	0.1 ± 0.3	0.0 ± 0.2
Trail B errors	0.6 ± 0.7	1.1 ± 1.5	0.6 ± 0.8	0.8 ± 1.2
Digit Span Backwards	4.0 ± 0.8	4.2 ± 1.1	4.2 ± 1.1	4.2 ± 0.9
Stroop Interference	43.8 ± 7.9	44.9 ± 9.1	48.5 ± 8.9	49.9 ± 9.1
Stroop Errors	0.8 ± 0.8	0.8 ± 0.8	0.4 ± 0.6	0.3 ± 0.7
Naming – Total	13.3 ± 0.9	14.0 ± 4.2	13.9 ± 0.8	14.2 ± 0.8
Fluency (letter P, total)	12.2 ± 4.3	12.0 ± 3.8	14.5 ± 4.1	12.6 ± 4.4
Fluency (number of phonemic clusters)	2.6 ± 1.4	2.3 ± 1.6	3.5 ± 1.4	3.1 ± 1.3
Fluency (size of phonemic clusters)	6.7 ± 3.8	5.2 ± 3.9	9.2 ± 3.7	7.1 ± 2.8
Fluency (switching of phonemic clusters)	7.6 ± 3.8	8.5 ± 3.3	8.2 ± 3.7	8.6 ± 3.2
Fluency (number of semantic clusters)	1.9 ± 1.0	1.5 ± 0.9	2.7 ± 1.3	1.7 ± 1.3
Fluency (size of semantic clusters)	4.5 ± 2.6	3.7 ± 2.8	6.5 ± 3.2	4.0 ± 3.1
Fluency (switching of semantic clusters)	8.7 ± 3.5	9.4 ± 3.0	10.2 ± 4.1	8.8 ± 5.2

Legend: Paired T test was used to compare means; multiplicity-adjusted p-value was non-significant in all comparisons

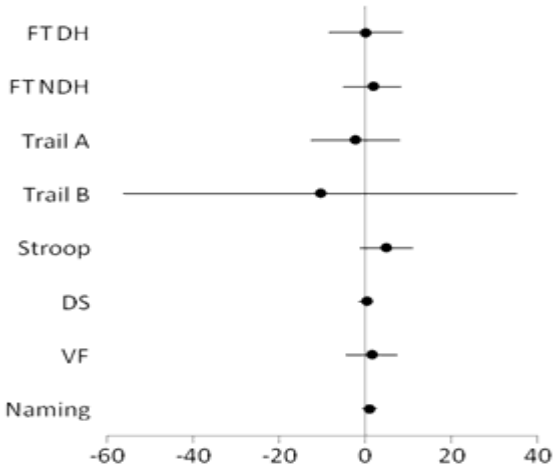
2.3 - Cognitive performance analysis – The estimated practice or learning effect

The average difference between the second and the first applications of each test is depicted in table 1, and represents the estimated practice or learning effect of the whole population (migraine and controls), as no differences were documented between groups in any test. The test-retest reliability and the 90% confidence interval for each averaged difference in test scores are presented in table 3 and graphic 1. These values represent limits above or below which one can infer a likely change in the status of the patient.

Table 3 – Average Practice or Learning effect and 90% CI of raw scores of the tests including in the battery

	Interclass Correlation Coefficient	**Average Practice Effect**	**90% CI**
Finger tapping (dominant hand)	0.712	**0.03**	- 8.59 to 8.65
Finger tapping (non-dominant hand)	0.797	**1.60**	- 5.15 to 8.36
Trail A Time	0.645	**-2.43**	- 12.72 to 7.86
Trail B Time	0.526	**-10.48**	– 56.14 to 35,19
Digit Span Backwards	0.769	**0.10**	-1.45 to 1.66
Stroop Interference	0.533	**4.85**	- 1.34 to 11.05
Naming – Total	0.573	**0.85**	-0.80 to 2.50
Fluency (letter P, total)	0.152	**1.42**	-4.55 to 7.39

Graphic 1 – Expected improvement by practice effect in each test



Legend: Lines represent average raw scores ± 90% CI; FT DH – Finger tapping Dominant Hand; FT NDH – Finger Tapping Non-Dominant Hand; DS – Digit Span; VF – Verbal Fluency

DISCUSSION

Migraine related disability measurement mostly relies on patients' self-report of ictal dysfunction; some instruments already exist that include measurement of interictal burden and health-related quality of life related to migraine(131). Part of the migraine-related disability may be related to cognitive symptoms, either interictally or during attacks. Cognitive dysfunction may contribute to patients' perception of being only 46% effective when working during migraine(92) or to the increased frequency of cognitive complaints amongst migraineurs.

We assembled a short test battery, easily applicable in any clinical setting and focused on executive functions and language, in order to obtain a quantitative measurement of cognitive dysfunction related to migraine. We then set up to determine if migraneurs in their interictal status would perform differently in this battery when compared to matched healthy controls.

Testing this battery produced different measures that may pinpoint different aspects of cognitive functioning during the attacks. Executive functions have been specifically studied in the interictal period of migraineurs without aura. All the previous studies that focused only on executive measures documented a decline in migraineurs compared to controls in test such as the trail B and Wisconsin(59), in alternate finger tapping (210), in visual-spatial SWITCH task(203) and in the Boston Scanning Test and Controlled Oral Word Association Test (but not in Trail B) (211). The differences were related to length and severity of the disease(59), and to reduced middle frontal gyrus GM density(203) but not to the presence of white matter lesions on MRI(211). In our study, migraine patients' performance outside attacks was not statistically different to the performance of controls in all test scores, including the trail B. This is in accordance with Le Pira(211), but in disagreement with Carmarda(59). Likewise, in our study we have found no difference between groups in all composite or derived scores (237, 277) and test-retest variance, suggesting that both overall performance but also cognitive strategies may not be much different between migraine patients outside an attack and controls.

Most larger studies with broader testing (evaluation of several cognitive domains, and including some executive measures) were either negative in documenting interictal executive dysfunction in episodic migraine without aura(105, 159, 184, 219, 269, 270,

280, 281) or showed very small and trivial changes (105, 282, 283). Our results are therefore in line with previous data. Differences to previous studies focusing on interictal executive function in migraine without aura may relate to interindividual variations, sampling and sample size, co-morbidities (such as vascular risk factors, anxiety and/or depression) and concomitant use of migraine prophylactics (59, 105, 203, 210, 211, 284). Our sample is of otherwise healthy and young migraineurs, with low impact disease without migraine prophylactic medication.

Having determined that this battery will not differentiate migraineurs in the interictal status from controls, its potential usefulness would be restricted to the identification and quantification of migraine attack-related disability, which implies its' repeated application. Its usefulness in such context would depend on the magnitude of its practice effect bias and on the determination of the clinically meaningful change in test scores, in repeated applications.

We tested participants performance in a repeated short term (average 45 days) applications and we were able to demonstrate a slight score improvement towards the second evaluation, as described in most neuropsychological tests, corresponding to the practice effect(279, 285). The magnitude of this effect in our sample was as expected in healthy controls.

Executive tests are slightly less susceptible to practice(285), as their objective is to evaluate problem solving strategies, speed and attention. With repeated applications, strategies learned can change and attention may be shifted, influencing practice but, on the other hand, are more easily influenced by performance variability(286). We need to consider this effect in identifying meaningful changes of performance in sequential battery applications, to distinguish improvement on test performance (due to practice and familiarity) from improvement due to changes in intrinsic cognitive ability. As an example, Trail and verbal fluency tests were demonstrated to have scarce learning effects over 12 months, but that was not held true for other executive tests(287). In our study, the improvement in one particular test– the Stroop test –was found to be significant between applications, when considering the total sample, but did not differ between groups. This improvement could not be accounted by any of the clinical variables considered, including depressive symptoms. The Stroop test differed from other tests by showing higher test-retest reliability, thus justifying that small individual

changes may have been sufficient to establish a statistical difference between test applications, in our small sample.

We were able to quantify the expected improvement due to the practice effect for each test of this battery, using a predefined standard methodology (279), in order to be able to correctly interpret individual variation and to identify a meaningful change. These calculations were made for each test, using the raw test scores, because variability in learning differed between tests.

In conclusion, we assembled a short and practical battery that was not able to identify interictal cognitive performance changes in otherwise healthy migraine patients without prophylactic treatment, when compared to age, sex and literacy matched controls. We were able to determine the expected practice effect for each of the battery tests and to identify the tests more likely to improve. This data can allow further studies in which we will be able to correctly interpret variations in sequential short term applications of this battery in different migraine status, such as during an attack. We recognize this instrument needs to be tested during a migraine attack, in order to determine if it is applicable, if it is able to identify cognitive dysfunction and if it correlates to other measures of cognitive difficulties, such as subjective *ad hoc* assessment or to the Mig-SCog(118) and to attack related disability. Such an instrument, if performing adequately, could be used as an objective end-point in acute treatment migraine trials(190), besides simple pain relief and recurrence. Further studies may therefore be needed, in larger samples and in more complex migraine populations, such as frequent migraine with need for prophylactics, chronic migraine or migraine with psychiatric co-morbidities.

An Arterial Spin Labeling MRI perfusion study of Migraine without aura attacks.

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An Arterial Spin Labeling MRI perfusion study of Migraine without aura attacks.
[submitted]

ABSTRACT

Background: Studies of brain perfusion during attacks of migraine without aura are scarce and have inconsistent results.

Objective: To study global brain perfusion during a spontaneously occurring untreated migraine without aura attack using Arterial Spin Labeling (ASL) MRI.

Methods: Prospective study of migraine patients scanned with ASL-MRI during a spontaneous untreated attack and in a headache free period. Image analysis used FSL and MATLAB; Group analysis used permutation methods in order to identify voxels with statistically significant perfusion differences between migraine and migraine-free sessions.

Results: Thirteen women were scanned, with an age average of 35.7 years and average disease duration of 23 years. The evaluated migraine attack had an average intensity of 6.8 (VAS) and an average duration of 16 hours. No global or regional perfusion differences were identified in the attack, when compared to the baseline scan.

Discussion: This is the first study of brain perfusion during attacks of migraine without aura using the ASL-MRI technique. Our results substantiate that the painful phase of migraine without aura attacks does not involve significant changes in brain perfusion.

INTRODUCTION

Brain functional imaging has led to a wider understanding of neuronal processes involved in non-structural disorders, such as migraine and other headache syndromes; the migraine attack remains the hallmark of migraine and the basis for understanding its clinical impact and pathological processes.

The study of brain perfusion during the migraine attack has yield controversial information. Initial perfusion studies measured regional cerebral blood flow (rCBF) with ^{133}Xe and were the basis of the vascular theory of migraine. In migraine with aura, a biphasic pattern with hypoperfusion during the aura phase and hyperperfusion during the headache phase(288) was identified with this technique. The studies of the visual aura have ever since been associated with a cerebral posterior hypoperfusion wave that spreads anteriorly, which is consistently documented in ^{133}Xe, SPECT, PET and perfusion perfusion-weighted imaging (PWI) MR(289).

Over 80% of migraine patients suffer from migraine without aura. These patients have been scarcely studied and the results of such studies have been inconsistent(290-292), with only one PET study being able to identified a reduction in CBF and CBV during headache yet without changes in oxygen extraction(293).

We aimed to evaluate brain perfusion changes during headache in patients with migraine without aura, using a non-invasive quantitative MRI perfusion technique, Arterial Spin Labelling (ASL-MRI), which presents both high temporal and spatial resolutions and is sensitive to the perfusion changes occurring at the capillary level(294, 295). In this study we will measure the global and regional brain cerebral blood flow twice, once during a spontaneous attack of migraine without aura and later in the same patients, while headache-free.

METHODS

Population

Volunteers were recruited among the hospital staff by internal mail and intranet advertisement and in the acute care outpatient clinic by screening of the triage nurse.

We included otherwise healthy adults (20 to 45 years) with episodic migraine without aura. The presence of aura, other headaches or headache frequency >15 days per month were exclusion criteria, as well as pregnancy, claustrophobia or the presence of ferromagnetic foreign bodies or metallic implants or devices. In order to minimize potential effects of pharmacological agents, the only allowed daily medication was oral contraception. There was no financial compensation for the volunteers. All volunteers signed a written informed consent. The study protocol was approved by the Hospital Ethics Committee.

Study design

Prospective longitudinal study with two evaluations of the same individual in two conditions, first during a spontaneously occurring migraine without aura attack and another in a headache free period, within a minimal interval of 48 hours since the last attack. Acute pain medication was not allowed in the 12 hours before the attack evaluation. A minimal headache intensity of 4 on a VAS was required to be eligible for the attack evaluation and scanning could be done in any time within the attack, as long as pain intensity wasn't decreasing; attack duration was not a limitation. In the post-hoc analysis we compared characteristics of patients scanned early and late during the attack, using the frame of the first five hours for the early attack, as it encompasses the average duration of the attacks studied in previous series.

Both evaluations consisted of a brief interview collecting demographic and clinical details of headaches and of the evaluated headache, followed by the MRI scan. Data collected included ICDH-III diagnosis, gender, age, literacy, disease duration, usual frequency, duration and intensity of attacks, use of prophylactic treatment and other current treatments and description of the evaluated attack; migraine impact was quantified with the HIT-6(140) score and the presence of depressive symptoms with the Beck Depression Inventory(274).

Image Acquisition

Volunteers were studied on 3 Tesla Siemens Verio MRI system (Siemens, Erlangen, Germany) using a 12-channel head RF coil. Subject's motion was restricted

with foam padding between the head and the coil. For each subject, a T1-weighted structural image (3D T1 MPRAGE, TR=2250m, TE=2.26ms, voxel size of 1x1x1mm^3) and PASL (Q2TIPS technique; PICORE labeling scheme; 2D echo planar -GE-EPI- readout, TR=2500ms, TE= 11ms, TI1 = 700ms, TIs= 1600ms, TI2= 1800ms, with 9 contiguous axial 8mm thickness slices with a voxel resolution of 4 x 4 x 10mm^3 were acquired in an ascending order baseline images) were obtained during rest.

Image Processing and Analysis

Image analysis was performed using FSL (http://fsl.fmrib.ox.ac.uk/)(296) and MATLAB custom based tools (The MathWorks, Inc., USA). ASL data pre- processing included brain extraction(297), motion correction(298), temporal filtering with a 100s frequency cutoff and spatial smoothing with a 5mm full width half maximum (FWHM) Gaussian kernel. Data were also co-registered to an expanded functional image, to a main structural image and to a standard space using the FSL tool FLIRT(298). Subsequently, control and labeled images were pairwise subtracted and perfusion weighted maps were computed by normalization with the brain equilibrium magnetization estimated from the averaged control images. Nine regions of interest (ROI) were identified according to the MNI152 atlas (McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada) and group averaged CBF values were assessed for each ROI and session.

Statistical Analyses

Statistical analysis of clinical variables was made with SPSS 20.0. Comparison of means between the two study evaluations used the paired t-test; in post-hoc analysis comparison of means between groups the independent sample T-test was used. CBF variation was calculated by subtracting the total CBF on the baseline session from the total CBF of the migraine attack (attack CBF – baseline CBF = ΔCBF) and by averaging the ΔCBF to the baseline CBF (ΔCBF/ baseline CBF = ΔCBF %). Multiple linear regression was used to determine in any independent variable, either population related (age, literacy, disease duration, HIT-6 and time lapse between evaluations) or attack related (pain duration and intensity of pain, nausea, photophobia, phonophobia and aggravation with

physical effort) had influence on the ΔCBF (dependent variable). Type I error was set at the two-sided 1% significance level.

RESULTS

1. Population

Fourteen right-handed female patients were included yet one patient dropped out. The final sample of 13 females had an age average of 35.7 ± 7.4 years. Previous medical history was positive for asthma in one patient and 6 were mild smokers (less than 10 units per day). Six (46%) used oral contraception; no other medication was currently being taken. Average Beck score was 5.0±3.6, all patients scored within normal values.

Average migraine duration was 22.7±10.2 years. The HIT-6 score was 62±4.0, representing a high impact disease. Average monthly attack frequency was 2.3±1.6 (1 to 6) with an average duration of 32.6±25.3 hours and average intensity of 7.4±1.3 on a 0-10 VAS scale. Patients described unilateral(54%), predominantly throbbing pain always accompanied by photo, phonophobia and nausea, 4(31%) vomited regularly in attacks and 11(85%) had pain aggravation by physical effort.

2. Migraine attack evaluation and comparison with baseline

Details of the evaluated migraine attack are depicted on table 1.

Table 1 – Characterization of Baseline and Attack variables

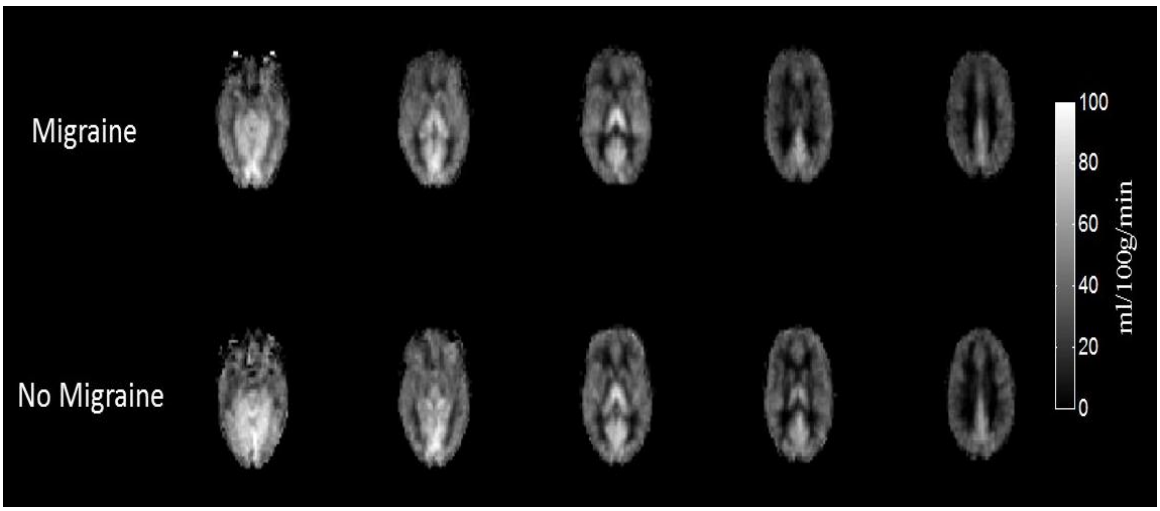
Subjects	BASELINE		MIGRAINE ATTACK						
			PAIN			Ass. Symptoms			
	HIT-6	Total CBF	Total CBF	Dura-tion	Inten-sity	Nau-sea	Photo-phobia	Phono-phobia	Worse P. Effort
1	68	45,0	44,1	7,67	8,0	4,0	3,0	7,0	4,0
2	64	33,7	27,5	24,17	6,0	2,0	3,0	3,0	2,0
3	63	42,3	39,1	2,67	6,0	4,0	2,0	2,0	4,0
4	60	32,5	30,4	69,00	5,0	4,0	4,0	4,0	3,0
5	65	41,5	35,1	9,67	9,0	6,0	8,0	8,0	9,0
6	60	46,9	45,6	45,70	8,0	5,0	5,0	0	0
7	52	45,2	52,1	13,25	6,0	3,0	5,0	5,0	6,0
8	60	46,0	40,5	6,25	8,0	5,0	7,0	7,0	6,0
9	59	50,6	57,0	5,00	9,0	5,0	5,0	6,0	6,0
10	62	42.4	41.7	4,00	5,0	6,5	6,5	8,0	8,0

11	65	37,8	40,9	6,67	7,0	5,0	5,0	5,0	5,0
12	63	36,5	36,8	4,50	6,0	1,0	5,0	5,0	2,0
13	65	50,8	51,1	12,00	6,0	5,0	5,0	5,0	5,0
Av ± sd	62 ± 4	42.4 ± 6.2	41.7 ±8.8	16.2 ±19.7	6.8 ± 1.4	4.7 ± 1.5	4.9 ± 1.7	5.0 ± 2.3	4.6 ± 2.5

Legend: HIT-6 – Headache Impact Test (in points); CBF – Cerebral Blood Flow (in ml/ 100g/ min); Duration – Pain duration up to the scan (in hours); Intensity – Pain intensity upon entering the scan (0-10 VAS); Nausea - Nausea intensity upon entering the scan (0-10 VAS); Photophobia - Photophobia intensity upon entering the scan (0-10 VAS); Phonophobia - Phonophobia intensity upon entering the scan (0-10 VAS); Worse with P. Effort – Intensity of pain aggravation by physical effort upon entering the scan (0-10 VAS); Av ± sd – average ± standard deviation

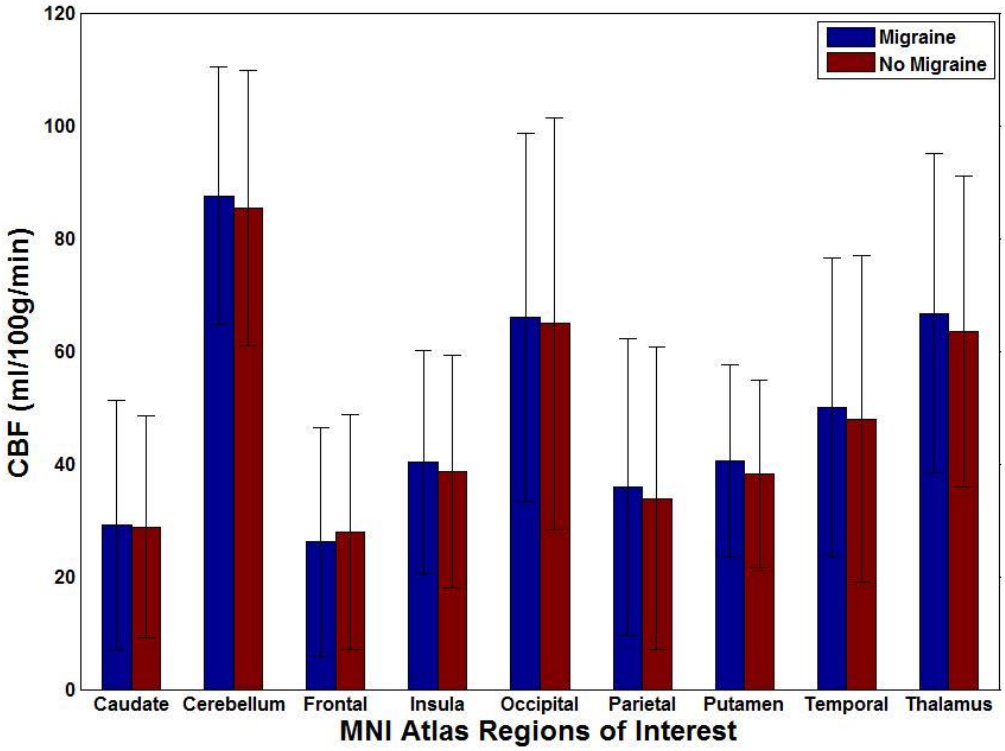
The average attack intensity was similar to usual attacks (paired T-Test 0.959, p=0.357 n.s.); all patients had nausea and photophobia on the evaluated attack, 2(15%) vomited and all but one(92%) had photophobia and pain aggravation with physical effort. Average total CBF values during the attack were similar to total CBF values outside the attack (41.7±8.8 versus 42.4± 6.2 ml/100g/min, p=0.589, n.s.); Perfusion weighted maps across subjects comparing migraine and non-migraine sessions are plotted for total CBF (Figure 1).

Figure 1 – CBF maps averaged across subjects during the Migraine Attack and Attack free status



Legend – CBF maps averaged across subjects in both conditions (Migraine Attack and Attack free status), for six representative slices in MNI standard space.

Figure 2 – CBF of different regions of interest (ROIs) during the attack and attack free status



Legend: Group average per session; Bars represent the mean, error bars the standard deviation of the mean. No differences were found in any comparison (paired T-test, p *n.s.*)

CBF analysis in several regions of interest was compared and no differences were found in any of the analyzed regions (Figure 2).

3. Post-hoc analysis

CBF variation (ΔCBF %) represented an average -2.25 ± 10.6 % of CBF in the attack relative to baseline (ranging from –18.4 to 15.3%). ΔCBF average value was -0.72±4.46 ml/100gr/min, ranging from -6.40 to 6.90. Multiple linear regression failed to identify any independent variable influencing ΔCBF (table 2).

Table 2 **-** Multiple Linear regression to evaluate the effect of clinical (independent) variables on Δ CBF (dependent variable)

	Δ CBF (DEPENDENT VARIABLE)	
INDEPENDENT VARIABLES	Unstandardized beta coefficient ± Std. Error	p
1. Population Related Variables		
Age (years)	-0.270 ± 0.203	0.232
Literacy (years)	0.163 ± 0.403	0.701
Disease Duration (years)	0.255 ± 0.131	0.100
HIT-6 score	-0.708 ± 0.346	0.087
Time between evaluations (days)	0.023 ± 0.023	0.351
2. Attack related Variables		
Attack duration (hours)	-0.027 ± 0.141	0.854
Pain intensity (VAS)	0.076 ± 2.416	0.976
Nausea Intensity (VAS)	-0.377 ± 2.462	0.884
Photophobia Intensity (VAS)	-0.307 ± 1.662	0.861
Phonophobia Intensity (VAS)	-0.317 ± 1.666	0.857
Worsening with P. Effort (VAS)	0.490 ± 1.967	0.813

Legend: p = significance level;

Table 3 **–** Post-Hoc analysis 1 - Comparison of clinical variables of patients scanned early (≤ 5h) and late (> 5h) into the attack

	Early attack (≤ 5h) N=4	**Late attack (> 5h) N=9**	*P*
	Mean ± sd	Mean ± sd	
Age (years)	33.0 ± 7.6	36.9 ± 7.4	0.402
Literacy (years)	16.2 ± 3.3	15.1 ± 3.4	0.583
Disease Duration (years)	22.2 ± 11.1	22.9 ± 10.5	0.923
HIT-6 score	61.8 ± 1.9	62.1 ± 4.7	0.888
Pain intensity (VAS)	6.5 ± 1.7	7.0 ± 1.3	0.577
Nausea Intensity (VAS)	4.1 ± 2.3	4.3 ± 1.2	0.833
Photophobia Intensity (VAS)	4.6 ± 1.9	5.0 ± 1.6	0.724
Phonophobia Intensity (VAS)	5.2 ± 2.5	4.9 ± 2.4	0.810
Worsening with P. Effort (VAS)	5.0 ± 2.6	4.4 ± 2.6	0.729
Attack total CBF	44.3 ± 11.1	40.8 ± 8.5	0.578
Δ CBF	1.2 ± 4.8	-1.3 ± 4.4	0.425

Legend: sd – standard deviation; p = significance level;

Due to the wide variation of scan timing and the range of ΔCBF values, patients evaluated early (≤ 5 hours, n=4) and late (>5 hours) into the attack and patients having positive (migraine attack>baseline, n=5) and negative ΔCBF (baseline>migraine attack) were compared; no significant differences were identified (tables 3 and 4).

Table 4 – Post-Hoc analysis 2 - Comparison of clinical variables of patients with negative and positive ΔCBF

	ΔCBF < 0 (Baseline > Attack) N=7 Mean ± sd	**ΔCBF > 0 (Baseline < Attack) N=5** Mean ± sd	*p*
Age (years)	35.4 ± 6.0	37.8 ± 9.1	0.597
Literacy (years)	15.3 ± 3.3	15.6 ± 3.9	0.883
Disease Duration (years)	18.0 ± 8.7	30.0 ± 9.6	0.047
HIT-6 score	62.0 ± 3.1	60.8 ± 5.5	0.424
Pain intensity (VAS)	7.1 ± 1.5	6.8 ± 1.3	0.695
Nausea Intensity (VAS)	4.3 ± 1.2	3.8 ± 1.8	0.590
Photophobia Intensity (VAS)	4.6 ± 2.2	5.0 ± 0.0	0.629
Phonophobia Intensity (VAS)	4.4 ± 3.0	5.2 ± 0.4	0.525
Worsening with P. Effort (VAS)	4.0 ± 2.9	4.8 ± 1.6	0.592
Baseline total CBF	41.1 ± 5.8	44.2 ± 6.8	0.423
Attack total CBF	37.5 ± 6.8	47.6 ± 8.4	0.044
ΔCBF	-3.6 ± 2.3	3.4 ± 3.2	0.001
ΔCBF %	-9.2 ± 6.2	7.5 ± 5.0	0.001

Legend: sd – standard deviation; p = significance level;

DISCUSSION

No significant brain global or regional CBF changes were identified in this study, using ASL-MRI to scan 13 migraine without aura attacks, in line with most of existing data(290-292, 299). Our findings support that brain perfusion changes are a marker of migraine with aura being most likely driven by the a neurogenic CSD-like phenomena, which is able to influence the neurovascular unit and decrease regional cerebral blood flow(48). These changes do not seem to occur in attacks without aura.

Initial ^{133}Xe perfusion studies in migraine with aura demonstrated hyperperfusion during headache, after the initial reduction in blood flow of the aura

(288, 300-303). These were supported by SPECT studies, although rCBF increases shown after the aura were not clearly timed to pain onset (303, 304). Findings of ^{133}Xe studies in attacks without aura are discrepant, some revealing increase in mean CBF during headache(305-309) while most showed no differences(292, 299, 310). This raised the hypothesis of different pathophysiology of the two types of attacks(311, 312) as the visual aura is consistently associated with a progressive postero-anterior hypoperfusion wave (CBF variation of −10 to −35%)(291) using different techniques(289).

Migraine is a heterogeneous disease and several differences exist between attacks with and without aura(311); different clinical manifestations may represent phenotypic differences of the same disorder, resulting from genetic and environmental variance, or be synonymous of distinct pathophysiology. Although cortical involvement by CSD-like phenomenon has been elegantly demonstrated in visual aura with BOLD-fMRI (40, 48), other attack-related phenomena independent of aura could also potentially translate into brain perfusion changes, such as activation and sensitization of the trigemino-vascular system and of other cortical and subcortical areas specifically involved in migraine pain modulation(48).

Studies of brain perfusion during attacks without aura are scarce; to our best knowledge six were published in English literature, comprising 56 patients(290-293, 299, 313) and using ^{133}Xe(313) CT, Xe-SPET, PET and dynamic susceptibility contrast perfusion weighted image (DSC-PWI) MRI. Most of the patients (N=32) were studied with Xe-SPECT(290, 292, 299) and only one had a global hyperperfusion during the headache. Studies with ^{133}Xe(313) in two patients identified focal oligemia in different regions in each (occipitoparietal and parietocentral). PET was used to study 9 patients and a slight reductions in CBF (up to 10%) and CBV (up to 5%) during headache were identified, although with normal oxygen extraction(293). The most recent study included 13 patients scanned with PWI-MRI and was completely negative(291).

These results are not uniform, but the majority of the patients studied had no detectable perfusion changes during attacks without aura. The 12 cases in which perfusion differences were identified, those were mild and below the range found in aura(293) or inconsistent(313). The incongruence of these results could be associated with patient selection, timing of the scan, measurement reproducibility and technique limitations. Timing of the scan is a particularly important aspect, as a recent PET study in migraine without aura has identified brain regional blood flow differences in the premonitory phase of a triggered migraine attack (before pain) when compared with the painful phase, as well as different patterns of activations with the evolving attack(28).

ASL-MRI allows quantitative measurement of CBF with high temporal and spatial resolutions(294) being sensitive to the perfusion changes occurring at the capillary level(295), which reflects more closely the changes taking place at the neurovascular unit(294). ASL uses an endogenous diffusible tracer (water molecules of the blood) to estimate the brain perfusion(294), being non-invasive and showing high reproducibility and accuracy for quantitative CBF values, compared to other techniques(314). The major drawbacks of ASL perfusion studies are its low signal-to-noise ratio (SNR, 1% of signal change), requiring the use of high field MRI units (as was used in the this study) and the inadequate CBF quantification in cases of significant delays in the arterial arrival time, such as in patients with extracranial atherosclerotic disease (an unlikely problem in our population)(315).

There are four patients reports of attacks studied with ASL-MRI, three of auras revealing reversible focal hyperperfusion in areas corresponding to the aura symptoms(316); one patient without aura was scanned very early (1h into pain) and a bilateral thalamic and hypothalamic hypoperfusion was shown, associated with relative frontal cortex hyperperfusion; changes reversible 30 minutes after treatment with a triptan, correlating with headache “improvement” (317). The ASL findings in this single case report are not consistent with our results, maybe resulting from timing of the scan or treatment effect.

Some reports of hypoperfusion changes similar to those observed during auras were documented in attacks without aura, in 2 patients with ^{133}Xe(313) and in one with PET(318). Visual changes atypical for aura were also associated with brain hypoperfusion (using PET and BOLD-fMRI)(319, 320), findings that have led to the speculation that CSD-like events could also occur in attacks without aura, although no robust scientific evidence supporting these claims exists(48). A most likely explanation is probably that aura related neuronal changes and associated hypoperfusion could sometimes be clinically silent, as often happens in epilepsy patients that have sub-clinical seizures. Some early cases of hypoperfusion waves (^{133}Xe and PWI-MRI studies(291, 303)) in migraine with aura attacks that persisted into the headache phase after the disappearance of the aura are supportive of this view. An alternative hypothesis could relate to some minor clinical symptoms occurring in attacks, such as the "visual snow" phenomena, could be caused by mild CSD-like changes that did not evolve into full auras but are still be a marker of brain metabolism changes related to higher susceptibility of having aura(321).

All patients in our sample had migraine without aura and long lasting disease (on average 22 years) being therefore unlikely to develop aura-like phenomena in the future. The attack studied was representative of their usual attacks, both in pain intensity and associated symptoms. We obtained a high impact episodic migraine sample population free of preventive treatment with a similar size to the larger published series (n=13) and studied an untreated attack, avoiding biases related to the effects of triggering substances or treatments. The timing of image acquisition in our sample was 16.2±19.7 hours (from 2h40 to 69 hours), later than previous studies of spontaneous attacks: Bednarczyk scanned patients with PET between 3.8 and 24.5 hours (average 3.3h)(293), Sanchez del Rio with PWI-MRI between 1 to 11h (average 4h30 ± 2h50)(291), studies with ^{133}Xe SPECT included scans in the first 30 to 60 minutes(299), within about 1 hour (292) and from 3h to 20h (average 7h±5h)(299). We were unable to find changes in the subgroup of patients scanned early (<5 hours) and this sub-group was in all aspects similar to the group scanned later; although with the inherent limitations of a post-hoc analysis in a small sample, our data suggests that timing of acquisition had no influence on results.

We did not impose any limit to the duration of pain in our study, allowing patients to come as soon as they felt that they needed treatment in order to reach a moderate pain intensity in order to ensure that the scan evaluated a fully symptomatic attack and to avoid the late premonitory phase(28), although bearing in mind that variability occurs between patients and attacks and that there is no relevant clinical marker that allows the identification of attack phases. Nevertheless, available evidence suggests that no significant perfusion changes are expected in neither phase of untreated migraine without aura attack (292, 299, 310).

Our study has limitations inherent to the used technique, yet it should be emphasized that the major limitation (the arterial arrival time differences) should not be an issue in the population studied. Relevant aspects include the potential low magnitude of perfusion changes occurring during attacks could have falleen in-between the limits of the reproducibility of the technique (less than 10% CBF change)(322) and a potential bias induced by the expected circadian variation of CBF values(323) could have been relevant in this sample, as it was no not possible to scan each patient at the same schedule in the two studies.

Although being one of the largest patient series published, our study still had a small sample size. It has been suggested that a cohort of less than 15 patients would be enough to obtain valid results(324) however, if we consider that migraine heterogeneity could relate to the existence of different subgroups of patients, our patient series may not have be sufficient to identify such subgroups. Our post-hoc analysis, separating patients with positive and negative ΔCBF was unable to identify meaningful differences to allow subgroup characterization. Post-hoc analyses performed in this study imposes further limitations of results' interpretation. Finally, we recognize that the scanning time, imposed by our study design, was heterogeneous within the attack, although it did not seem to influence results.

In conclusion, our results support previous findings suggesting that no major brain perfusion changes occur during the headache phase of the migraine without aura attack, in contrast with the consistent posterior hypoperfusion related to migraine aura.

Executive function in migraine without aura attacks.

An fMRI study using the N-Back paradigm.

Gil-Gouveia R, Pinto JS, Figueiredo P, Vilela PF, Martins IP.
Executive function in migraine without aura attacks. An fMRI study using the N-Back paradigm. [in preparation]

ABSTRACT

Background: Migraine attack-related reversible cognitive dysfunction is characterized by an attention and working memory impairment and slower processing speed. The neuronal subtract underling this changes is unknown but involvement of the anterior cingulate and the fronto-polar cortex in possible, as both structures are active in pain processing and during migraine attacks.

Objective: To explore cortical activation in response to a working memory task (N-Back) in migraine patients in and outside migraine attacks.

Methods: A BOLD-fMRI study and a brief neuropsychological evaluation focused on executive functions were conducted in episodic migraine patients during an untreated spontaneously occurring migraine without aura attack and repeated in a headache-free period. Brain activation patterns and neuropsychological performance were compared between the two situations.

Results: Thirteen female migraine volunteers were studied, with an age average of 35.7 years. The evaluated migraine attack had an average intensity of 6.8 (VAS) and an average duration of 16 hours. No changes in neuropsychological performance nor relevant disruption of cortical oxygen consumption while performing the working memory task were identified in the attack, when compared to the baseline scan.

Discussion: This study was not able to demonstrate a group difference neither in neuropsychological performance, brain activation patterns or areas between the migraine attack and the headache-free status thus failing to provide an explanation to attack-related cognitive symptoms in migraine.

INTRODUCTION

Migraine patients describe reversible subjective cognitive changes during migraine without aura attacks that contribute to migraine attack-related disability. Neuropsychological evaluation supports an attack-related reversible performance decline when compared to baseline performance, although the pattern of dysfunction has been inconsistent across studies (108, 109).

The most often described spontaneous symptoms are attention difficulties, diminished cognitive efficiency and processing speed impairment, which are nicely correlated to evidence of an attack-related attention and working memory deficit and of impaired processing speed obtained in studies focusing on neuropsychological executive measures (60, 96, 97, 100, 102, 108).

Attention can be defined as the ability to focus on a task relevant stimulus and is believed to be mediated by anterior cingulate cortex (ACC) function(325); working memory represents the ability to temporarily store task relevant information and has been associated with fronto-polar cortex (FPC) activity(326). Processing speed is not a cognitive function that can be attributed to a specific brain area, it depends on functional and effective interactions among distant brain regions involved in the execution of different cognitive functions(327).

Involvement of the cingulated and prefrontal(29, 53, 153, 214, 215) cortices (as well as other cortical and subcortical structures) has been consistently documented by PET during migraine without aura attacks being generally attributed to modulation of pain sensory input and in the cognitive processing of pain perception(153).

An increased ACC activation in episodic migraine patients responding to trigeminal noxious stimulation has been interpreted as analgesic compensatory reorganization of pain-processing regions(328); in fact, migraine chronicity (as well as other chronic pain conditions) has been related to a decrease in ACC grey matter(172), a probably adaptive phenomenon that is partially reversible with effective pain treatment(329-331).

Structural abnormalities have also been documented in interictal episodic migraine without aura patients, such as reduced middle frontal gyrus and inferior

parietal lobe grey matter density(203) and reduced connectivity of the fronto-parietal(executive) network (FPN)(170), supporting the involvement of the executive system in migraine.

All these findings are probably related to involvement of the general pain processing brain network in migraine yet the evidence of functional implication of these brain changes in actual cognitive performance is scarce(170, 203). In particular, no evidence of relation to attack-related cognitive dysfunction exists.

Our objective was to study the cortical activation pattern using fMRI and executive neuropsychological performance in response to an executive challenge during and attack of episodic migraine without aura and to compare it to the headache-free status. The fMRI paradigm chosen was the verbal N-Back, a working memory task that also involves attention and processing speed, and is able to activate the prefrontal, premotor, dorsal cingulate and posterior parietal cortices(332), some of the areas involved in migraine without aura attacks.

METHODS

Population

Volunteers were recruited among the hospital staff by internal mail and intranet advertisement and in the acute care outpatient clinic by screening of the triage nurse. We included otherwise healthy adults (from 20 to 45 years) with episodic migraine without aura (ICDH-III(7)). Exclusion criteria were the presence of aura, other headaches types, headache frequency >15 days per month, pregnancy, claustrophobia or the presence of ferromagnetic foreign bodies or metallic implants or devices. The only allowed daily medication was oral contraception. There was no financial compensation for the volunteers. All volunteers signed a written informed consent. The study protocol was approved by the Hospital Ethics Committee.

Study design

This was a prospective longitudinal study with two evaluations of the same individual in two conditions, first during a spontaneously occurring migraine without aura attack and another in a headache free period, within a minimal headache-free

interval of 48 hours. Eligibility for the attack evaluation implied a minimal headache intensity of 4 on a 0-10 VAS and the absence of acute pain medication in the previous 12 hours.

Both evaluations consisted of a clinical interview including detailed headache history followed by the application of a short neuropsychological battery and the MRI scan, which included structural high resolution T1-weighted 3 Tesla MRI and the fMRI N-Back paradigm(333).

Tests included in the neuropsychological battery were Finger Tapping (233) (motor speed), Trail Making Test(237) (attention, shift), Stroop Test (interference task)(239) (processing speed, inhibitory control), Reverse Digit Span(245) (verbal working memory), phonemic (Letter "p") verbal fluency(275) (verbal initiative, monitoring and semantic memory) and naming of 5 compound nouns from the Aachen Aphasia Test(276) (noun retrieval). Migraine impact was quantified with the HIT-6(140) score and the presence of depressive symptoms with the Beck Depression Inventory (273, 274). The Mig-SCog was used to evaluate the impact of cognitive symptoms during the migraine attack(118).

In the N-Back paradigm we used the 2-Back task, in which a sequence of letters is displayed one at a time and subjects are asked to determine if the current letter was the same as that presented 2 letters previously. The control condition was the search for a pre-specified target (ex. "find the letter "A"). Each block had 21 letters presented in a pseudorandom sequence for 1 second each and an interstimulus interval of 1 second (total duration of 42 seconds); the ratio of target stimuli to distracter stimuli was 1:4 Five blocks of task/control were presented so the total task had a duration of 420 seconds (7 minutes).

Monitoring of N-Back performance included scoring correct, false positive and false negative answers. The attack evaluation also included scoring of migraine related symptoms (pain, nausea, photophobia, phonophobia, aggravation by physical effort and cognitive efficiency) intensity on a 0-10 VAS.

Image Acquisition

Volunteers were studied on 3 Tesla Siemens Verio MRI system (Siemens, Erlangen, Germany) using a 12-channel head RF coil. The participants were made familiar with the scanner and the NBack task was explained and trained before the scan. Subject's motion was restricted with foam padding between the head and the coil. For each subject, a T1-weighted structural image (3D T1 MPRAGE, TR=2250m, TE=2.26ms, voxel size of 1x1x1mm^3). BOLD images were obtained during the execution of an N-Back task, using a gradient-echo EPI sequence (TR=2000ms/TE=30ms). 22 slices were acquired with voxel size of 4x4x3 mm^3.

Image Processing and Analysis

Image analysis was performed using FSL (http://fsl.fmrib.ox.ac.uk/)(296, 334) and MATLAB custom based tools (The MathWorks, Inc., USA). BOLD data pre-processing included brain extraction, motion correction, temporal filtering with a 100s frequency cutoff and spatial smoothing with a 5mm FWHM Gaussian kernel. Data were also co-registered to a main structural image (MPRAGE) and to a standard space (MNI 2mm). BOLD responses were modeled by a block design with specific timings of the NBack task convolved with a double gamma HRF and entered into a General Linear Model (GLM). Standard motion parameters, temporal derivatives and temporal filtering of the regressor were also added to each individual GLM. Voxelwise parameters were obtained from the GLM coefficients over the cluster-thresholded ($p<0.05$ and $Z>2.3$) mask, for each subject.

Group analysis was performed on the individual contrasts of parameters using mixed effects, in order to identify voxels exhibiting statistically significant N-back-related BOLD signal changes. Group analysis was also performed in order to identify voxels exhibiting statistically significant BOLD differences between migraine and non-migraine sessions across subjects. Only voxels exhibiting statistically significant N-back-related BOLD signal changes were considered for the session comparison.

Effects of individual measures such as age, education, age of migraine onset, attack average duration, and migraine average frequency were added as additional explanatory variables. These where masked with the main contrast (mean). Voxelwise parameters were obtained from the GLM coefficients over the cluster-thresholded

($p<0.05$ and $Z>2.3$) mask, for each of the mean sessions, whereas effects of individual measures were obtained using uncorrected $p<0.05$ thresholding.

Group analysis was also performed in order to identify voxels exhibiting statistically significant BOLD differences between migraine and non-migraine sessions across subjects. Additional effects of physiological tests performed previously to the scanning (Stroop Test, Trail Test, Finger tapping with dominant hand and Finger tapping with the non-dominant hand) were also added as explanatory variables and these were contrast masked with the main contrast (difference between sessions).

Statistical Analyses

Statistical analysis of clinical variables was made using SPSS 20.0. Descriptive data included frequencies and central tendency measures; comparison of means between the two study evaluations was performed using the paired t-test. The Holm-Bonferroni step down procedure(278) was adopted to account for multiple testing and to provide strong control of the type I error at the two-sided 5% significance level. Reported p-values are adjusted for multiplicity using the Holm-Bonferroni correction(206). Multiple linear regression was used to determine in any independent variable, either population related (age, literacy, disease duration, HIT-6 and time lapse between evaluations) or attack related (Mig-SCOg, pain duration and intensity, intensity of nausea, photophobia, phonophobia, aggravation with physical effort and cognitive impairment) had influence on the tests that showed significant difference between evaluations (dependent variables).

RESULTS

Fourteen right-handed female patients were included yet one patient dropped out before completing the study. The final sample of 13 females had an age average of 35.7 ± 7.4 years. Previous medical history was positive for asthma in one patient and 6 were mild smokers (less than 10 units per day). Six (46%) used oral contraception; no other medication was currently being taken. Average Beck score was 5.0 ± 3.6, all patients scores were within normal values.

Average migraine disease duration was 22.7 ± 10.2 years. The HIT-6 score was 62±4.0, representing a high impact disease. Average monthly attack frequency of our sample was 2.3 ± 1.6 (range 1 to 6) with an average duration of 32.6±25.3 hours, having an average intensity of 7.4 ± 1.3 on a 0-10 VAS. Patients described unilateral(54%) predominantly throbbing pain always accompanied by photophobia, phonophobia and nausea; 11(85%) had pain aggravation by physical effort, 4 (31%) vomited regularly and 4 reported osmophobia regularly.

The studied migraine attack had an average pain duration of 16.2±20 hours (range: 2.6 to 69 hours) and an average pain intensity of 6.8±1.4 on a 0-10 VAS, similar to usual attacks (paired T-Test 0.959, p 0.357 n.s.). All patients had nausea and photophobia on the evaluated attack; 2 (15%) patients vomited, although the average nausea intensity was 4.7±1.5 and of photophobia 4.9±1.7, on a 0-10 VAS. All but one patient (92%) had phonophobia and pain aggravation with physical effort, with an average intensity of 5.0±2.3 and 4.6±2.5 respectively. Attack-related decrease in cognitive efficiency plotted on a 0-10 VAS was 5.3±2.6 on average and the Mig-SCog average score was 5.1±2.5 (range 2 to 11).

The average time between evaluations was 74.4 ± 61.6 days (range 36 to 275 days). Average raw scores and differences of neuropsychological tests performed in both evaluations are depicted in table 1.

Table 1 – Results of neuropsychological tests in both evaluations and mean difference of raw scores (second-first) between evaluations

	1st Evaluation (migraine)	**2nd Evaluation (headache free)**	**Mean Difference (2nd-1st)**	**p†**
Finger tapping (dominant hand)	49.6 ± 8.6	55.1 ± 5.0	5.6 ± 7.4	p 0,19*
Finger tapping (non-dominant hand)	43.9 ± 6.5	47.5 ± 4.4	3.6 ± 4.6	p 0,015*
Trail A Time	25.1 ± 4.3	22.5 ± 5.4	-2.6 ± 5.4	p 0,981
Trail B Time	70.7 ± 19.1	60.6 ± 17.0	-10.1 ± 16.6	p 0,576

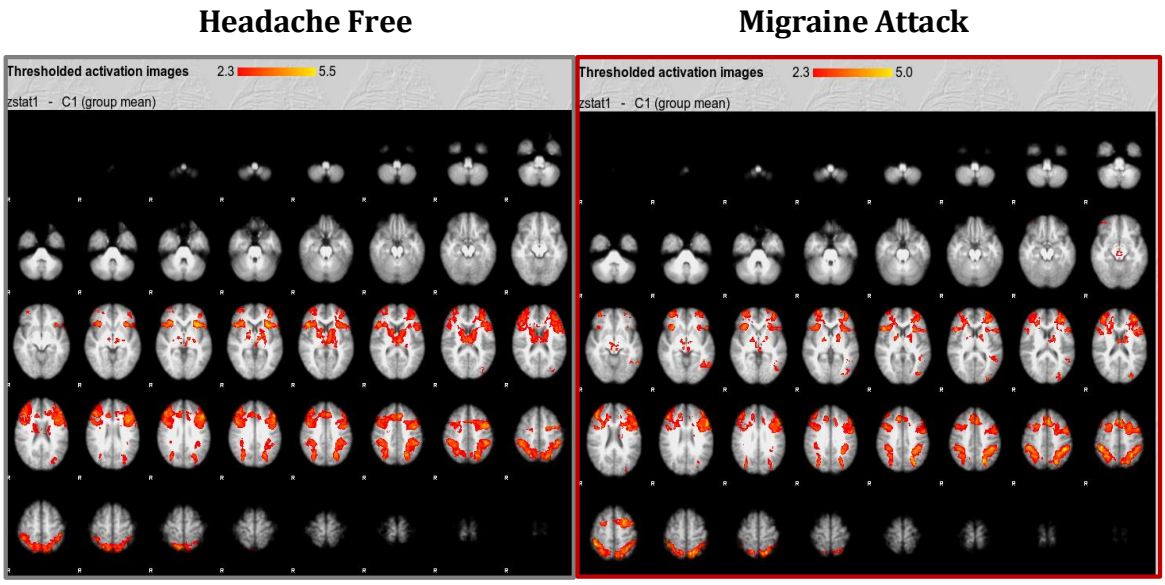
Trail difference (B-A)	45.6 ± 17.6	38.0 ± 16.0	-7.5 ± 15.6	p >0.99
Trail A errors	0.4 ± 0.6	0.2 ± 0.4	-0.2 ± 0.8	p >0.99
Trail B errors	0.3 ± 0.6	0.8 ± 0.9	-0.5 ± 1.1	p >0.99
Digit Span Backwards	4.6 ± 1.2	4.5 ± 1.5	-0.1 ± 1.0	p 0,794
Stroop Interference	55.4 ± 13.0	64.5 ± 11.0	11.1 ± 10.9	p 0,039*
Stroop Errors	0.8 ± 0.8	0.5 ± 0.5	-0.2 ± 1.0	p >0.99
Fluency (letter P, total)	14.8 ± 4.6	15.3 ± 5.0	0.5 ± 4.8	p >0.99
Naming – Total	13.3 ± 1.3	13.5 ± 1.0	0.0 ± 0.1	p >0.99
fMRI NBack – Correct answers	21.6 ± 2.4	23.5 ± 2.2	1.4 ± 2.7	p >0.99
fMRI NBack – Wrong answers	4.3 ± 2.8	3.2 ± 2.9	-1.1 ± 3.1	p >0.99

Legend: Av ± sd – average ± standard deviation; Paired T-Test was used to compare means; †p multiplicity-adjusted p-value; (*) p<0.050 was considered significant

Two tests showed an increase in performance from the attack to the baseline evaluation, the finger tapping (dominant hand 5.6 ± 7.4 score increase, p=0.019 and non-dominant hand 3.6 ± 4.6 score increase, p=0.015) and the stroop interference task (11.1 ± 10.9 score increase, p=0.039). The practice effect bias of short term repeated application of this battery was quantified in a previous study. For the Stroop interference task, the average expected score improvement is 4.85 (90% CI -1.34 to 11.05) so our observed value falls in the upper end of the 90% CI. For the finger tapping task, the average expected score improvement was 0.03 (90% CI -8.59 to 8.65) and 1.60 (90% CI -5.15 to 8.26) for the dominant and non-dominant hand respectively, so our observed values are within expected improvement. Linear regression failed to identify any influence of any of the studied disease or attack related variables to the performance improvement in the finger tapping and stroop tasks.

Three subjects were removed from further analysis due to motion (R9, R12 and R14). N-Back task showed an increased BOLD signal in both conditions in bilateral dorsolateral and ventrolateral prefrontal cortex and frontal poles, frontal lateral and medial premotor cortex, lateral and medial posterior parietal cortex and bilateral thalamus. (Figure 1)

Figure 1 – N-Back activation patterns outside and during the Migraine Attack

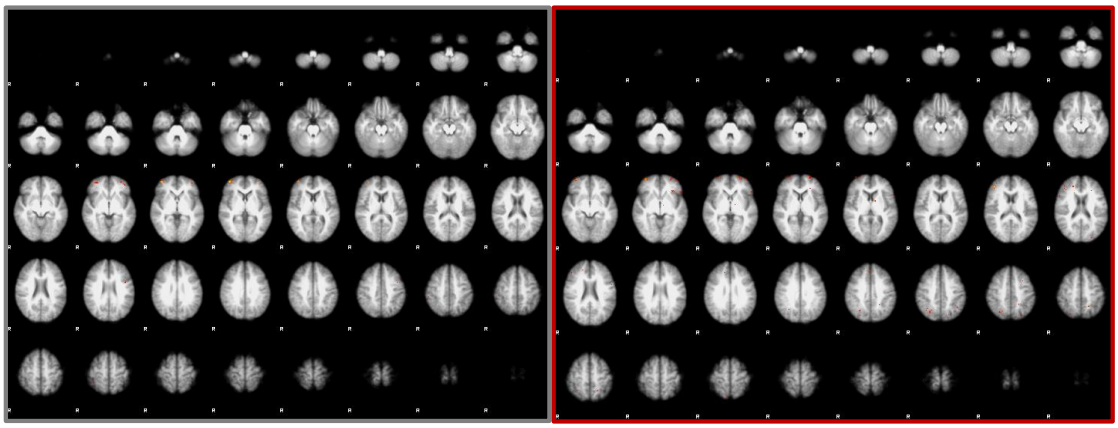


Legend: Activation maps for the N-Back task (versus control task) in migraine patients while headache-free and during a migraine attack. Regions of activation are color coded, cluster corrected ($Z>2.3$, cluster $p<0.05$). Areas activated in both situations include bilateral dorsolateral and ventrolateral prefrontal cortex and frontal poles, frontal lateral and medial premotor cortex, lateral and medial posterior parietal cortex and bilateral thalamus.

No significant differences were found between N-Back pattern activation in migraineurs during the migraine attack when compared to themselves while headache free, as plotted in the subtraction activation images - Figure 2.

Figure 2 – N-Back subtraction images

Headache Free > Migraine Attack **Migraine Attack > Headache Free**



Legend: Subtraction maps for the N-Back task activations between headache status: Headache free > Migraine attack and Migraine attack > headache free. Regions with differences of activation between conditions are color coded (uncorrected, $p<0.05$).

Age, literacy, disease duration, attack frequency and performance on the stroop, trail and finger-tapping tasks had no effect on BOLD activation patterns.

DISCUSSION

This study was not able to demonstrate disruption of cerebral activity associated with the execution of a working memory task during a migraine without aura attack.

We were able to study spontaneous occurring migraine attacks of moderate to high pain intensity and in which patients subjectively rated their attack-related cognitive efficiency in 5.3 (out of 10) and obtained robust activations of our areas of interest, the anterior cingulate and fronto-polar cortex, in both conditions with the N-Back paradigm, as expected(332). Our assumption was that the involvement of the cingulated and prefrontal cortex in migraine without aura attacks (29, 53, 153, 214, 215) could act as an internal interference disrupting the working memory construct therefore changing the pattern of brain activation in response to the N-Back paradigm and impairing task performance(335). An alternative hypothesis was that the increased workload imposed to this system by the competing stimulus (migraine attack and N-back task) would

induce an increase in fMRI signal in these areas(88, 336) regardless of task performance. We therefore hoped to investigate the neuronal subtract underling the attack-related migraine executive dysfunction(108) yet we were unsuccessful in demonstrating a group difference neither in activation patterns nor areas between the migraine attack and the headache-free status. Existent evidence supports the existence of attack-related cognitive dysfunction in migraine, with a fairly consistent pattern of executive functions impairment (108, 109, 284). In addition, involvement of executive brain structures is found in experimental pain studies(264) and chronic pain conditions are able induce brain neurochemical and neoplastic reorganization in cognitive related systems(87, 89). Our target structures, the ACC and FPC seem to exert top-down control to primary sensory processing areas in order to modulate information coming from several sensory stimuli(325, 326), including pain(264). In healthy volunteers cognitive engagement has been shown to reduce pain-related activity but cognitive-related activity was not altered by simultaneous pain stimuli although it increased the brain areas involved in the cognitive activity(88).

Our data supports that migraine attack-related cognitive dysfunction is not associated with relevant disruption of cortical oxygen consumption; migraine associated cortical metabolic changes in cognitive related brain areas probably falls into the range of physiological variability of cortical function. If true, the study of functional connectivity would have been more appropriate to identify a system imbalance in this experimental setting.

However, a number of limitations exist that may interfere with interpretations of these findings, the most important is probably the data analysis. Our option was to try to identify a group difference, assuming that topographic consistency of activation across subjects would be high, in order to make small VOIs meaningful with a small sample size; by doing so, we might have missed individual activity pattern variations. Also, we scanned attacks of heterogeneous durations (from 2.6 hours up to almost 3 days) and so brain activation patterns could be obscured in grouping different phases of the attack(28). A final issue relates to test-retest reliability, as this study used two sequential scans; repeatability of the selected N-back task seems to be fairly consistent in terms of pattern of activations (qualitatively) yet quantitative analysis (mean activation amplitudes and number of activated voxels) is not as reliable(337).

We additionally screened these patients for executive performance using a short neuropsychological battery (encompassed the domains of attention, processing speed, mental flexibility, monitoring and inhibitory control, working memory and verbal initiative and fluency) and monitoring N-Back response accuracy, although it correlates weakly with brain activation(337). Patients performed equally in the majority of tests both within a migraine attack and while headache-free. A performance improvement from attack to headache free was identified on the finger tapping and stroop interference tasks that were within the range of the expected practice effect for this tests. Executive dysfunction has been documented during migraine attacks in task of attention, processing speed, working memory and visuo-motor processing on computerized tests (60, 96, 97, 102). The conventional stroop and trail(219) as well as the other executive tests included in this battery have not been able to demonstrate performance decline neither during migraine attacks(109) nor in headache-free migraine patients compared to matched controls. Demonstrating executive dysfunction can be difficult, as there is almost no specific task to a given executive function nor there is a specific mapping to each brain function. Nevertheless patients consistently describe cognitive symptoms during attacks and in their subjective experience feel cognitively impaired, despite weak evidence of actual objective impairment.

Despite having mostly negative findings, this study has some strengths – it adds to the scarce fMRI data available about spontaneous occurring migraine attacks. Testing during attacks is difficult as migraine episodes are unpredictable while planning an fMRI is complex and time consuming(338). Because the attack scan is difficult to obtain, we always scanned the attack first, in order to minimize attrition. This induced a practice effect bias of repeated testing(225, 228) that we had to control for.

Another strength was the ability to include a homogeneous sample of otherwise healthy episodic migraine without aura patients with a long standing high impact disease but nevertheless without important confounders of cognitive function such as chronic medication (including headache prophylaxis) or depression, a sample that mirrors high impact community dwelling patients. As all the patients included were females, we cannot generalize to male patients nor to chronic headache patients.

In conclusion, our data supports that brain activation during performance of a working memory task is not disturbed by the neuronal processes associated with an

acute migraine without aura attack. Further work needs to be ensued to identify brain mechanisms subsiding patients subjective attack-related cognitive complaints.

5. Long Term Cognitive Dysfunction in Migraine

CHAPTER FOREWORD

The final chapter relates to the potential persistence or long term effects of migraine related cognitive (executive(59)) dysfunction, in analogy to other chronic or recurrent pain conditions.

To study the effects of persisting headache and migraine in older adults (over 50) a cross sectional survey using an extensive neuropsychological battery was conducted in a large sample of community dwelling individuals and their performance was compared between headache diagnoses, finding slight differences in some of the applied measures of executive function both in migraine and in non-migraine headache patients, compared to controls. These findings argue for an interictal effect of recurrent pain (either migraine or non-migraine headache) on executive functions.

To explore if these differences could relate to an increased risk of cognitive decline, a follow up study with neuropsychological revaluation of the same sample was undertaken after 5 years. Rate of cognitive decline was not found to differ between migraine, non-migraine headache and control patients supporting that older adults with persisting headaches and migraine do not have an increased risk of cognitive impairment nor dementia.

Migraine, Headaches and Cognition.

Martins IP, Gil-Gouveia R, Silva C, Maruta C, Oliveira AG.

Migraine, headaches and cognition.

Headache 2012 Nov-Dec; 52(10):1471-82 Impact Factor: 3.19;

ABSTRACT

Objectives and Background: The possible effects of migraine on executive abilities remain controversial, hence we studied inter-ictal cognitive performance of individuals with migraine and non migraine headaches (NMH) compared to headache free controls.

Design and Method: In a cross sectional observational study, taking place in primary care, adults aged 50 or above were evaluated by a neurobehavioral battery including several executive measures. Present history of headache was sought and migraine was diagnosed by the ID-Migraine questionnaire. Effect of headache type on cognitive measures was analysed with multiple regression with adjustment by diagnosis, age, gender, education and depressive symptoms.

Results: Among 478 participants 23.2% reported current headache of whom 50 NMH and 61 migraine. No group differences were found in the majority of cognitive measures. Compared to controls, migraine subjects performed worse on a test of attention, while NMH participants presented more intrusions and worse discriminability in memory recognition plus a lower performance on semantic memory tests.

Conclusion: The presence of headaches in late adulthood was related to a worse performance on few measures of executive functioning, suggesting that cognitive impact is not specific to migraine but might be associated to headache.

Introduction

Migraine is a highly prevalent brain disorder characterized by recurrent attacks of severe headache associated with nausea or vomiting. During attacks, patients are sensitive to all sensory stimuli and experience cognitive symptoms, often beginning before the headache itself (40, 157). They feel distracted, unable to concentrate or reason at their usual speed, and have difficulty performing mental tasks and retrieving names (115, 283, 339), symptoms that might suggest a dis-executive disorder. These manifestations may contribute to the impairment associated to the attacks and influence patients quality of life (340). Moreover, there is some controver*sy* regarding their inter-critical and long term persistence.

The study of inter-ictal cognitive abilities in migraine has produced inconsistent results. While some authors found disturbances involving the executive functions(60) either in migraine patients in general, or in specific migraine subgroups, such as those with severe attacks, patients with aura (59) and children (267), others were unable to find any difference between subjects with and without migraine (183, 184, 272, 281, 341).

The consistency of executive-like symptoms reported during attacks and deficits observed between the attacks could indicate a disturbance of the frontal lobes, exacerbated and becoming symptomatic during the attacks. That hypothesis received support from the finding of decreased grey matter density in the frontal and parietal lobes in 25 migraine patients compared to matched controls (203). The presence of subcortical white matter lesions, that are more common in migraine and headache sufferers than controls (341) could also be a possible explanation for the executive deficits but has been ruled out, at least in two studies. One study that excluded participants with such findings (203) and another (281) that controlled age related cognitive decline for that specific variable, did not find a negative effect of white matter lesions on cognition.

An alternative explanation for migraine-associated cognitive impairment is pain itself. The experience of chronic, or chronic recurrent pain, could interfere in the activity of some frontal networks that are shared by the pain matrix. Although most clinical and

brain imaging data (36, 40, 303, 318, 342) point to the participation of the occipital cortex in migraine rather than the fronto-subcortical networks subserving executive functions, several regions of the frontal cortex participate either in the pain matrix or in pain modulation (343). The orbitofrontal cortex, for instance, participates in inhibition and habituation to pain and has been shown to be dysfunctional in migraine, particularly in those with long duration of disease (344). According to this hypothesis, the executive dysfunction should not be exclusive to migraine but also apply to other conditions of chronic pain.

Due to the high prevalence of migraine in the general population(16) this question may be particularly relevant. Normal ageing is related to some decline in executive abilities (345) and a functional re-organization of the frontal lobes (346). Thus, migraine and other primary chronic headaches might be studied as contributing to, or risk factors of, long term age-related cognitive changes. Although a recent study comparing cognitive performance of migraine and headache patients with controls found no differences in visual perception and memory, it failed to explore most measures of executive functioning, apart from processing speed (281).

To disentangle these two hypotheses, i.e. that executive changes are specific to migraine or due headache pain, we compared the inter-ictal cognitive performance between adult and elderly individuals with or without headaches and migraine, focusing on different measures of executive functioning included on a comprehensive battery of neurobehavioral tests, controlling the effects of possible confounders.

Methods

The present study is part of an ongoing larger project dedicated to the effect of ageing in cognition. Baseline data of this project was analysed in a cross sectional observational design. Participants are adult individuals, with a minimum age of 50 years attending eleven primary health care centres of the National Health Service. Inclusion was made on a volunteer basis and participants were first screened and invited to participate by their GPs. Subjects were excluded if they had any known present or past history of a central nervous system disorder, namely stroke, brain injury, epilepsy,

dementia (known or suspected), psychosis, or a severe medical disorder like uncontrolled cancer, HIV infection, renal or hepatic failure or if their score on the Mini Mental State Evaluation (MMSE) (347) was below literacy-adjusted cut off point (348). Before being enrolled in the study, patients were required to give their informed consent. The study protocol was approved by the Ethics Committee of the Lisbon Faculty of Medicine.

Procedures

Patients were invited to participate during their regular medical appointments. After informed consent, participants undertook the MMSE and GP's filled a checklist of vascular risk factors (hypertension, diabetes and dyslipidemia).

Neuropsychological evaluation was then scheduled so that participants could be in their best conditions, not under time pressure and without headache. The neurobehavioral battery included the following tests: California verbal Learning Test - 9 item version (349), Wechsler Memory Scale III version (WMS-III) Visual Reproduction and Faces I subtests (245), Trail Making Test (29), semantic (Foods and Animals) and phonemic (Letter "p") verbal fluency, Stroop Test (237, 239), Digit Span (245), Symbol Search (242), Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary and Matrix Reasoning subtests (350), Information (351, 352) and a Famous Faces Test(250) . The battery also included scales of depression (Geriatric Depression Scale) (353) and Subjective Memory Complaints (SMQ) (354). A more detailed description of the battery and targeted domains has been reported elsewhere (355).

Although the cognitive measures collected in this project covered different cognitive domains, in this study we focused mostly on measures of executive functioning. Therefore, in addition to executive tests primarily directed to executive functions, we computed measures from the memory tests that are known to be sensitive to frontal lobe dysfunction. Such measures were the following: mental flexibility as assessed by TMT B and B-A, the latter being considered a more pure measure of set shifting (237), inhibitory control (Stroop test interference task), working memory (digit span backwards), processing speed (TMT A and Symbol Search), abstract reasoning (WASI Matrix Reasoning subtest) and speed of word retrieval and monitoring (evaluated by two

semantic fluency tasks and one phonological fluency task, known to be more sensible to frontal lobe dysfunction(233) . Episodic memory and learning were also evaluated (CVLT immediate first recall, total learning over 5 trials, short delay recall after interference, 20-minute delayed recall and WMS-III delayed visual memory). Particular emphasis was given to measures of episodic memory with executive contribution: CVLT-9 resistance to proactive interference (List B recall), intrusions (false positives) in recognition, discriminability index, and response bias (356).

During the interview participants were asked whether they were currently suffering from headaches. Whenever the answer was positive, subjects undertook the ID-Migraine (357), a brief and effective questionnaire for the diagnosis of migraine in primary care(358) that has been translated and validated to Portuguese with 0.94 sensitivity and 0.60 specificity(359) , compared to the ICHD-II criteria(186). It consists of three questions regarding headaches experienced in the past 3 months: the first concerns pain intensity ("Do your headaches limit your ability to work, study, or do what you needed to do for at least 1 day?"), the second screens photophobia ("Does light bother you a lot more than when you don't have headaches?") and the third is directed to nausea ("Do you feel nauseated or sick to your stomach when you have a headache?"). Subjects were classified as suffering from migraine headaches whenever there was a positive answer to two or three of those questions. Participants who did not complain of headaches were considered headache-free controls, those that complained of headaches and did not filled any or just one of the three ID-Migraine questions were classified as non migraine headache (NMH) sufferers(358).

Statistical Analysis

Statistical analysis was performed with the SPSS package 19.0. The chi-square test was used to compare the distribution by gender and vascular risk factors (presence or absence of hypertension, diabetes and serum cholesterol above normal range) among the three study groups (participants with migraine, NMH and headache free controls). Differences between these groups in age, literacy and scales scores were tested with oneway ANOVA with post-hoc Tukey tests.

The impact of migraine or NMH on cognitive performance, controlling for the possible confounders (355), was evaluated by multiple linear regression analysis (MRA).

Scores obtained on cognitive measures under study were the dependent variables. Since the three subgroups were different in their demographic features (age, gender, literacy and depressive symptoms) it was not possible to compare directly their mean cognitive raw scores. Therefore, to analyze the influence of migraine and NMH on cognitive measures, controlling for possible confounders, repeated MRAs were performed on which the dependent variable was each cognitive measure and the independent variables were subjects' age, gender, literacy (divided in two groups, low education if equal or inferior to 4 years and basic to high education if equal or above five years), depressive symptoms (considered significant if equal or above 4 points in the GDS, and non significant if under that value).

Due to the multiplicity of analyses performed, in order to avoiding type I errors, the statistical significance level was adjusted to $p<0.01$. The distribution of the dependent variables involved in the model was tested and whenever normality was excluded the variables were dichotomized.

Results

The study population consisted of 479 volunteers; one patient was excluded due to incomplete fulfilling of the headache questionnaire. Of the 478 individuals included, 306 (64.0 %) were females and the age average was 66.44 $\pm$ 8.95 years (range: 50 to 95 years). The majority, 367 (76.8%) individuals, did not complain of headaches while 111 (23.2 %) were headache sufferers. Sixty-one participants (12.8 % of total sample) fulfilled the operational diagnostic criteria of migraine (MH). Twenty eight subjects reported two symptoms of the ID migraine and 33 all symptoms of this headache questionnaire. Fifty participants (10.5%) were classified as having NMH.

The frequency of headaches changed significantly by decade of age (Table 1) (Chi-Square = 21.65 (6), $p<0.001$). The frequency of migraine decreased between the 6th and the 8th decades of life while the frequency of non migraine headaches increased and the overall frequency of headache free individuals remained relatively stable.

Table 1- Migraine and non migraine headache frequency, by decade of age

Age range (in years)	No headaches (N=367) % (total number)	Non migraine headaches (N=50) % (total number)	Migraine (N=61) % (total number)
50-59 years	73.4% (80)	4.6% (5)	22.0% (24)
60-69 years	75.1% (148)	10.7% (21)	14.2% (28)
70-79 years	81.4% (105)	14.0% (18)	4.7% (6)
>80 years	79.1% (34)	14.0% (6)	7.0% (3)

As depicted in Table 2, headache patients were more often female than individuals without headache (Chi-Square=24.52 (1), p<0.0001). Migraine subjects, when compared to participants without headache and to those with NMH, were significantly younger (5 and 7 years younger, respectively), had a higher scores on the depression scale (GDS)(p<0.0001) and more subjective memory complaints (SMQ) (p<0.0001). There were no significant differences on these variables between headache-free individuals and those with NMH (Tukey HSD post-hoc test). There was a moderate correlation between GDS and SMQ score (Pearson r=0.475, p<0.0001). The three groups had different levels of literacy and participants with migraine had lower education than those without headache. There were no differences, among the three groups on the proportion of individuals with any of the vascular risk factors sought, either hypertension (X2= 2.88 (2), p= n.s.), diabetes (X2= .50 (2), p= n.s.) or high levels of total serum cholesterol (X2= 4.89 (2), p= n.s.) nor in the number of risk factors (X2= 7.11 (6), p=n.s.).

Table 2 – Population characteristics by diagnosis

	Without headache	Non migraine headache	Migraine	Chi–Square / ANOVA
N	367	50	61	
Gender (F: M)	213:154	37:13	56:5	P < 0.0001
Age (mean±sd)	66.8 ± 9.0	69.3 ± 7.9	**61.9** ± 7.6	P < 0.0001
Literacy(mean±sd)	**7.4** ± 4.3	6.3 ± 4.4	**5.8** ± 3.9	P = 0.007
GDS(mean±sd)	3.1 ± 3.3	4.0 ± 3.1	**5.4** ± 3.2	P < 0.0001

SMC(mean±sd)	5.7 ±3.5	5.9 ±3.1	**8.7**± 3.3	P < 0.0001

Legend to table 2: F= females, M= males; GDS= geriatric depression scale; SMC=subjective memory complaints; numbers in bold identify the group that is significantly different from others in the *pos hoc* test.

Table 3 – Multiple regression analysis

	Adjusted R Square	Migraine (B)	Non migraine headache(B)
		Difference to controls (means)	
Executive function tests and measures			
Stroop Interference	.304	-2.913	-1.135
Digit Span Backwards	.184	-.047	-.173
Trail A Time	.352	11.310	12.459
Trail B Time	.386	25.670	21.095
Trail difference (B-A)	.238	14.055	15.217
Fluency Animals	.216	-.099	-.172
Fluency Food	.141	-1.033	.340
Fluency Letter P	.204	.259	.160
Symbol Search	.397	**-2.438***	-1.104
Matrix reasoning	.252	-1.346	-1.113
Mazes (time)	.187	-.147	1.932
CVLT intrusions in recognition	.124	-.128	**1.139****
CVLT recognition discriminability index	.136	.636	**-3.531****
CVLT resistence to proactive interference (List B recall)	.130	.288	.504
CVLT response bias	.012	.008	.094
Other tests and measures			
CVLT first immediate recall	1.00	.204	.317
CVLT total learning (sum 1 to 5 trials)	.174	.531	.452
CVLT short term free recall	.166	-.020	-.108
CVLT delayed recall	.158	.303	-.295
CVLT recognition correct responses	.033	.082	-.026
WMS-III delayed visual memory	.259	.998	-4.086
WMS-III memory for faces	.163	-1.055	-.126
WASI Vocabulary	.386	-1.209	**-6.192****
Information Subtest	.345	-.170	**-1.488 ****
Famous faces test	.193	-.294	-.689

Legend to table 3: Multiple regression analysis. Independent variables included in each regression were: migraine, non-migraine headache, gender, age, literacy (low or medium to high), depressive symptoms (significant or nonsignificant score in GDS). Adjusted R Square represents the proportion of variance on each test score that is explained by the model; Significance level: * <.001; **<.0001; otherwise non-significant

Multiple regression analysis results are presented in Table 3. Few cognitive measures showed a significant association with the diagnosis of headache. Concerning executive functions, individuals with migraine had a lower score in Symbol search compared to controls. NMH participants, on the other hand, produced more intrusions in word list recognition (in CVLT-9) and had a worse recognition discriminability compared to controls. Mean scores obtained by participants with MH, NMH and controls in tests that showed significant differences were, respectively: intrusions in recognition (0.66 ± 1.10 in migraine patients, 2.32 ± 2.84 in participants with NMH and 1.11 ± 1.76 in controls, Anova F 12.36, p<0.0001); Symbol Search (15.33 ± 7.46 in migraine patients, 15.50 ± 7.64 in those with NMH and 18.31 ± 7.39 in controls, Anova F 6.44, p=.002) and CVLT recognition discriminability index (96.8 ± 4.35 in MH, 91.15 ± 8.85 in NMH and 94.8 ± 6.55 in participants without headache, Anova F 10.3, p<.0001). It is worth noticing that the mean scores presented above are raw scores, not adjusted for age, gender and literacy and therefore the differences presented here are less evident than those found on the regression analysis.

Neither migraine nor NMH had any impact on the performance of other cognitive tests and measures except for the language/semantic memory tests (Information and Vocabulary) where NMH subjects had lower performance compared to other groups. Their scores were respectively: Information (16.4 ± 2.87 in MH, 15.68 ± 3.45 in NMH and 17.79 ± 2.51 in participants without headache, Anova F 18,453, p<.0001) and Vocabulary (48,07 +14,38 in MH, 45,33+14,65 NMH,53,73+13,43 controls, Anova F 11,237, p<.0001).

Besides, there was an effect of subject's age in all measures, an effect of education in the majority of tests and measures and of gender in verbal memory (CVLT, reverse digit span) and food fluency. Severity of depressive symptoms had an effect in tests of attention (Trail A and B, but not B-A) and visual memory.

Discussion

The present study, aimed to detect the long term impact of migraine and other headaches on executive functioning and other cognitive abilities, produced mainly

negative results, which is reassuring for the large number of subjects that suffer from headaches most of their lives.

Indeed, this study showed that the presence of migraine or NMH in middle to late adult life did not modify significantly the vast majority of cognitive functions evaluated. Namely, it did not affect several tests of executive functions such as the verbal fluency tasks, working memory (digit span backwards) or inhibitory control (Stroop test). It also had no effect on measures of learning or correct recall in episodic memory (verbal or visual). These results are in agreement with studies performed in community-based cohorts of adult individuals (183-185, 269, 270), including a large study in twins (271), as well as with three longitudinal studies of adults, one of them including patients with aura (270, 272) that showed no decline over time on MMSE, memory visuo-perceptive and attention tests.

In the present study only a few tests were negatively influenced by the presence of headache. Migraine sufferers were slower in a task of sustained attention and processing speed (Symbol search test) a function related to the activation and integrity of the prefrontal cortex (360) and that correlates with cerebral health markers in the frontal lobes, as quantified by neuro-imaging. On the other hand, few tests were negatively influenced by NMH. These were related to semantic memory (Information and vocabulary) and executive functioning (recognition discriminability and the number of intrusions on memory recognition, both derived from the CVLT). Concerning the latter two tests, there is evidence that subjects with frontal-executive dysfunction are more likely to produce false positives or "intrusions" in memory recognition and to have a difficulty in discriminating targets from distractors. Those are measures of faulty retrieval strategies, poor source memory and are associated to a tendency to confabulate (361-364). Subjects with frontal lobe dysfunction tend to endorse semantically related distracters, which highlights their defective ability to inhibit irrelevant activations to select relevant activations(365). Although response bias has also been linked to frontal lobe lesions leading to a more liberal response set, i.e., tendency to answer "yes" (366), this was not affected in our sample of participants with headache, suggesting that there might be subtle differences among those measures.

However the performance in other tests of frontal-executive functioning was not significantly worse in migraine or NMH, namely the Trail Making Test-B possibly the test

most consistently found to be disturbed in individuals with migraine compared to controls (59, 280, 367).

Thus, the present results show that suffering from headache in late adult life may be associated with a worse performance in some executive tests, though not consistently among all measures, nor between different headache types. These changes do not seem specific to migraine.

Although these results are exploratory and their interpretation can only be tentative they raise the question of the possible role of headache or pain in cognition. Chronic or chronic recurrent pain causes disability and behavioural changes. Patients often withdraw from social, family, physical and professional activities, leading eventually to less cognitive stimulation, mental distress, learned helplessness, depression, sleep disturbances, analgesics or anti-inflammatory intake, just to mention a few. Thus, these different factors might influence cognitive functioning through different mechanisms (368) and may eventually lead to morphometric changes in the brain. Studies of individuals with other types of chronic pain, like chronic back pain, fibromyalgia, tension type headache and phantom limb pain have shown a decreased of frontal grey matter density (369-372).

It is difficult to explain the lower performance in test of semantic memory in subjects with NMH, particularly because these might be a heterogeneous group regarding headache diagnosis and duration. One may just speculate that hypothetical avoidance of social interaction due to headache might lead to less acquired knowledge, but this needs to be investigated in homogeneous groups of patients.

Pain is a multidimensional experience that involves somatic, visceral, cognitive and emotional domains. We do not assume that the frontal component of this matrix is directly related to pain intensity or localization, but rather that it is involved in the general pain experience. More research is necessary, in particular in other types of chronic pain and distress situations (e.g., psychosocial stress, mood disorders), to understand what may be the contribution of these different domains to executive functions.

Changes found in cognition and brain morphometry (373) in headache sufferers could also result from a functional adaptive strategy, or neural reorganization, developed to overcome repeated episodes of pain in a kind of scaffolding mechanism similar to that described in ageing (374). These grey matter changes in pain matrix

structures are probably cross-sectional to all chronic or recurrent pain syndromes (263) At least two studies have found a relationship between cognitive abilities and the severity or frequency of migraine attacks (219, 280, 373), and others found a relationship between the duration of migraine and grey matter density, reinforcing the idea that disease activity implies structural changes (263).

The observed cognitive changes could, alternatively, result from subcortical white matter hyperintensities that have been described in migraine (373, 375) and other chronic headache (341), but this has been dismissed in other studies (281). Besides in there were no differences in vascular risk factors between the groups that could explain a higher risk for subclinical ischaemic lesions in either group.

Finally, one can also hypothesize that primary headache can be a marker of the failure of the normal anti-nociceptive mechanisms, which require the participation of the frontal lobes, and both pain and cognition can be a consequence of that dysfunction. The finding of an orbito frontal dysfunction in migraine with aura, related to the duration of migraine, supports this hypothesis (344).

Another interesting finding of this study was that participants with migraine had a worse subjective perception of their cognitive abilities, presenting significantly higher scores on a questionnaire of subjective memory complaints, in spite of being significantly younger than other groups and not differing from controls on the majority of cognitive tests (namely in all memory measures). This was found in studies of chronic pain (376). The subjective complaints score correlated with depressive symptoms. This information is useful to give patients an explanation for their complaints and to decide upon pharmacological interventions that can be useful for both migraine and depression.

We acknowledge some limitations of this study. Firstly, the present results can only be applied to the presence of headaches above 50 years of age. Secondly, it only takes into account the present history of headaches, not its past history, severity and type (migraine with or without aura or other diagnosis). The presence of headache was inquired by a subjective question. This method does not guarantee that “without headache patients” are headache free; these subjects can have infrequent headaches that, eventually, might be migraine headaches. NMH were not characterized in detail and may constitute a heterogeneous group. Moreover migraine is known to change with age and to lose some of its typical associated features (377). Therefore it is possible that

among the NMH group there are also patients with age-modified migraine. Yet, so far there are neither specific criteria for migraine in advanced age, nor evidence supporting the use of another criteria (186) and at this point, we must consider that NMH participants have other headaches than migraine. Indeed, the demographic features of the migraine group were quite typical with a female predominance, younger age and associated depression (378-380) and the prevalence of headache and migraine by age reproduced the existing epidemiological data in the adult population (16, 381). This can be viewed as a measure of external validity of the ID migraine questionnaire used in the diagnosis of headache. The method used also does not differentiate between migraine patients with and without aura and excludes subjects with acephalgic migraine, although the latter is relatively rare compared to other migraine variants.

Thirdly, we also acknowledge that the battery used does not cover all domains of executive functioning and more studies are necessary to provide a fine grain analysis of those abilities in headache patients.

Yet, this study includes a large sample of subjects from primary care that was not selected because of headache, who were evaluated by an extensive battery of cognitive and behavioural tests and controlled for the presence and severity of co-morbidities and factors that might affect cognitive performance. The majority of studies demonstrating migraine-associated cognitive impairment were performed in small samples of subjects from migraine clinics or through community advertisement (59, 159, 219, 282, 283), which may produce a selection bias towards patients with the most severe or complicated forms of this disorder. In addition, this represents one of the few studies comparing migraine with other headaches, controlling for the effect of head pain. One study contrasted migraine with post-traumatic headache(219) and found differences in the latter, which can be expected following traumatic brain injury. Burker (382) compared migraine with NMH in a community setting yet recruited only young women, finding no differences in cognitive performance, Meyer (98) found reversible changes during attacks in migraine, cluster and chronic daily headache and Rist found no differences in age related cognitive decline in a period of 4 years(281) between headache patients and controls.

Conclusion. Age-associated changes of cognitive function, a major concern among persons that are expected to live beyond the eight decade, are overall not significantly

affected by the late presence of migraine or headache. Yet, the presence of headaches in late adulthood , and not just migraine, may have some impact on speed of information processing and few measures of executive function. More studies are required to understand if these findings are reproduced on longitudinal studies with a more detailed analysis of headaches and other types of pain.

Migraine, Headaches and Cognition.

A follow-up study on cognitive decline.

Gil-Gouveia R, Loureiro C, Martins IP.

Migraine, headaches and cognition – a follow-up study on cognitive decline. [in preparation]

ABSTRACT

Objectives and Background: Cognitive performance of older adults and elderlies with persisting headaches and migraine has been shown to differ from control individuals in some aspects of executive functioning yet the influence of persisting migraine and non-migraine headache on cognitive decline is controversial.

Design and Method: Older (>50 years) adults with migraine, non-migraine headache and healthy controls had an extensive neuropsychological evaluation at baseline and after 5 years, to screen for cognitive decline in memory and/or executive functions.

Results: From the original 478 individuals, 275 (57.5%) were evaluated, with an age average of 70.40±8.34 years, 64% being females. Cognitive decline occurred in 14.9% of the sample, yet neither migraine nor non-migraine headache influenced the odds of decline. In migraine patients, decline was not consistently associated with any migraine characteristic.

Conclusion: Persisting migraine and non-migraine headache at old age is not associated with an increase in probability of cognitive decline. Although chronic pain and aging are able to influence cognitive function, pain-related changes are probably due to pain adaptation mechanisms and not degenerative processes.

Introduction

The interaction between migraine and cognition is complex and dynamic. One its' most consistent aspect is the existence of attack-related cognitive symptoms(95, 118) which are substantiated by findings of reversible neuropsychological impairment in executive functions, memory and learning during attacks (108, 109) although the brain processes underling this phenomena still remain speculative.

Some patients also complain of cognitive changes outside attacks – cross-sectional controlled inter-ictal studies identify a negligible to small effect of migraine on visuomotor processing speed, attention, verbal learning and recall, working memory and sustained attention, sometimes more expressive in patients' subgroups, such as migraine with aura or severe migraine(104, 105). Inter-ictal brain perfusion changes on migraineurs have also been documented (280, 383) supporting the hypothesis that migraine associated white matter abnormalities and brain lesions(216, 384) could increase the risk of late-life cognitive impairment or dementia. However, evidence obtained from longitudinal studies, some with large samples and population-based, does not associate migraine to and increased risk of cognitive decline (185, 217, 270, 281) nor to the progression of such white matter abnormalities or infarct-like lesions(385). Furthermore, it is debatable if cognitive changes identified in migraine patients, regardless of the setting, are specific to migraine and/or headache or relate only to the experience of recurrent pain, in which executive and cognitive impairment has also been documented(89).

In a previous study we compared the inter-ictal cognitive performance of older adults and elderlies with or without headaches and migraine concluding that the vast majority of cognitive functions evaluated were uninfluenced by the presence of migraine or non-migraine headache at late adult life. However, a few tests were influenced by headache – both migraine and non-migraine headache patients performed worse in some of the executive tests, suggesting an effect of persistent recurrent pain in executive functioning(268). Executive abilities also show some decline with normal ageing (345) associated with functional re-organization of the frontal lobes(346).

In the current study we aimed to determine if persisting migraine and non-migraine headache has influence in cognitive decline, specifically in executive

functioning and/ or memory, by performing a 5 years follow-up revaluation if our initial patient cohort.

Methods

The present study is part of an ongoing larger project dedicated to the effect of ageing in cognition(386). Baseline data of this project was analysed in a cross sectional observational design; this follow-up study includes revaluation of the original sample after an average period of 5 years. Participants are adult individuals who gave their written informed consent, with a minimum age of 50 years at inclusion, attending eleven primary health care centres of the National Health Service. Participants were screened and invited to participate by their GPs; exclusion criteria included history of any neurologic or psychiatric disease (ex. stroke, brain injury, epilepsy, dementia or psychosis), any severe medical disorder with potential influence on neurological function (ex. metastatic cancer, HIV infection, renal or hepatic failure) or a Mini Mental State Evaluation (MMSE)(347) score below their literacy-adjusted cut-off value(348). The study protocol was approved by the Ethics Committee of the Lisbon Faculty of Medicine.

Procedures

Baseline cross sectional data retrieved upon inclusion was (1) medical history (MMSE, checklist of vascular risk factors, medication); (2) current headache status (without headache/ with headache) then further characterized into migraine(MH) or non-migraine headache(NMH), as defined by a positive or negative ID-Migraine(357) and (3) Complete neuropsychological evaluation along with scales of depression (Geriatric Depression Scale)(353) and Subjective Memory Complaints (SMQ)(354). Further details about this study have been reported elsewhere(268).

In the present study, the participants were submitted to complete neuropsychological revaluation, in order to screen for significant cognitive decline in the 5 years follow up. Test results were computed into Z-Scores using normative data

matched to gender, age and literacy. Cognitive decline was defined as a decrease superior to 1.5 standard deviations in the average Z-Scores of tests of memory and/or executive functions. Memory score was calculated by averaging the Z-scores of 2 memory tests (California verbal Learning Test 9-item version(349) and Wechsler Memory Scale III version (WMS-III)(245)); executive score was calculated by averaging the Z-scores of 5 executive tests (Trail Making Test a and B(29), semantic (Foods and Animals) and phonemic (Letter "p") verbal fluency). Scales of depression (Geriatric Depression Scale)(353) and Subjective Memory Complaints (SMQ) (354) were again included.

Patients with migraine headache (MH) at baseline were additionally contacted by telephone and systematically assessed for the current occurrence of headaches and details of headache history (disease duration, presence of aura, frequency and duration of attacks and headache impact, measured with HIT-6(140)).

Statistical Analysis

Statistical analysis was performed with the SPSS package 21.0. Descriptive statistics are presented as absolute and frequencies or mean ± standard deviation. Data was compared between the study groups (MH, NMH and headache free controls) with oneway ANOVA and post-hoc Tukey tests (for continuous variables) and chi-square tests for categorical variables.

In migraine patients the chi-square and independent sample T-test were used to compare patient variables as appropriate; the relation between the HIT-6 score and executive and memory scores was explored using the Pearson correlation coefficient. The statistical significance level was adjusted to $p<0.01$.

Results

The baseline study population included 478 individuals, 306 (64.0 %) females with an age average of 66.44±8.95 years (range: 50 to 95 years). As baseline, 367 (76.8%) patients were without headache (WH), 61 (12.8 %) had migraine (MH) and 50 (10.5%) non-migraine headache (NMH).

Two-hundred and three individuals(42.5%) were lost at follow-up – 109(23%) refused further participation, 53(11%) could not be reached or had moved, 3 had terminal illnesses and 15(3%) had died. Average follow up time was 58.9±7.2 months (~4.9 years), ranging from 40 to 70 months.

The follow-up study population included 275 individuals, 176 (64.0 %) females with an age average of 70.40±8.34 years (range 55 to 98 years). The headache diagnosis retained at follow-up included 216 (78.5%) subjects without headache (WH), 35 (12.7 %) with migraine (MH) and 24 (8.7%) with non-migraine headache (NMH). Retention rates were 58.9% in the group without headache, 57.4% in the migraine group and 48% in the non-migraine headache group. Demographic differences between groups are depicted in table 1.

Table 1 – Population characteristics by diagnosis

	Without Headache	**Non Migraine Headache**	**Migraine**	Statistics: Chi–Square Or Anova
N	214	24	35	
Gender (F(%):M)	126(60%):90	17(70%):7	33(94%):2	$\chi^2$17.430 (df2) p < 0.0001
Age Baseline (Mean±Sd)	65.8 ± 8.4	68.4 ± 6.8	**61.1** ± 7.4	F 6.741 p = 0.001
Age (Mean±Sd)	70.8 ± 8.5	73.0 ± 6.6	**66.1** ± 7.3	F 6.246 p = 0.002
Literacy(Mean±Sd)	7.8 ± 4.2	6.5 ± 4.4	6.1 ± 4.2	F 3.040 p = 0.049
GDS† (Mean±Sd)	**3.6** ± 3.2	5.2 ± 3.8	**5.9** ± 3.1	F 8.619 p < 0.0001
SMC(Mean±Sd)	6.2 + 3.7	6.3 + 4.1	**8.3** + 3.9	F 4.584 p = 0.010
Vascular risk factors 0 : 1 : 2 : ≥ 3	17: 48: 89: 57	1 : 4 : 10 : 9	4 : 6 : 19 : 4	$\chi^2$6.976 (df6) p = 0.323
Cognitive Decline (Yes(%):No)	33(15.3%):183	4(16.7%):20	4(11.4%):31	$\chi^2$0.416 (df2) p = 0.812
Executive Score (Mean±Sd)	0.086 ± 1.17	-0.226 ± 1.22	-0.049± 1.48	F 0.816 p = 0.443
Memory Score (Mean±Sd)	-0.090 ± 0.99	-0.136 ± 1.02	0.259 ± 1.08	F 1.914 p = 0.150

Legend: F= females, M= males; GDS= geriatric depression scale; SMC=subjective memory complaints; p≤0.010 was considered significant; numbers in bold identify the group(s) that is significantly different from others in the post hoc test; †GDS scores of migraine were different from those of patients without headache; non-migraine patients had no differences from migraine or without headache patients.

Similarly to the initial base line data, MH patients were more often females, were younger than NMH (by 6.7 years) and WH (by 4.7 years) and had more subjective memory complaints (SMQ) (p=0.011). The depression scale (GDS) scores differed between MH and WH (p<0.0001) while NMH patients had no differences from either of the other groups. The three groups had similar literacy. There were no differences, among the three groups on the proportion of individuals of the number of risk factors (table 1).

Cognitive decline was documented in 41(14.9%) of the revaluated sample, yet having migraine (χ^2= 0.383 (df1), p=0.536, n.s.) or non-migraine headaches (χ^2= 0.064 (df1), p=0.800, n.s.) had no influence on the decline rate when compared to the remaining sample. Headache or migraine also had no impact on the memory and executive scores (table 1).

From the 35 migraine patients (MH) included at baseline, 29(83%) were successfully interviewed about their headaches after the neuropsychological revaluation; 5 did not answer their phones and one died.

Nine patients (31%) reported having had aura with their headaches, although only one patient reported that all the attacks had aura. Eleven patients had had migraine for less than 20 years, 7 had had it from 21 to 50 years and 5 from 51 to 70 years; average HIT-6 score of this sample was 54.3 ± 11.1 (range 36 to 76).

Twenty patients had had migraine attacks in the last year, although in most, their frequency was scarce - 13(65%) patients only had up to one attack per monthly. Five (25%) patients had more than 15 monthly days with headache (chronic migraine), 2 of which had daily headache. Average attack duration was 17.9 ± 22.0 hours, ranging from 45 minutes to 3 days; one of the daily headache patients had continuous headache. Some patients changed their migraine characteristics at follow up, as 11(55%) ceased to have nausea with their attacks, 6(30%) ceased to be disturbed with photophobia and 7(35%) individuals were now able to work and function during their migraine attacks.

In patients with Migraine, having aura had no influence in cognitive decline (χ^2= 1.688 (df1), p=0.194, n.s.) nor on the executive (T= 0.639, p=0.529, n.s.) or memory

scores (T= -1.139, p=0.266, n.s.). The disease duration (χ^2= 7.256 (df6), p=0.298, n.s.), attack frequency (T= 1.291, p=0.213, n.s.), attack duration (T= 0.989, p=0.336, n.s.) and the presence of vascular risk factors (χ^2= 1.856 (df3), p=0.603, n.s.) had no association with decline in migraine patients.

Migraine patients showing a decline in cognitive functions were more likely to have a high HIT-6 score than those who remained cognitively normal (63.3±2.3 *versus* 53.1± 2.2, T=3.874, p=0.001) although the HIT-6 score did not correlate to the executive (Pearson -0.254, p 0.183) or memory scores (Pearson -0.032, p 0.867). These patients had lower literacy (4.0±0.0 *versus* 6.35± 4.6, T=-2.882, p=0.007) and were younger (59.2± 3.9 *versus* 67.0± 7.2, T=-2.108, p=0.043) than those who did not progress.

DISCUSSION

Our data supports that persisting migraine and non-migraine headache in older adults does not increase the risk of cognitive decline and does not influence performance in memory and executive tests.

All population-based longitudinal studies on the association of migraine with cognitive decline were also negative (185, 217, 270, 281, 385). The effect of non-migraine headache on cognition has only been studied in the Epidemiology of Vascular Aging (EVA) study(281, 341) that, similarly to our results and of findings in migraine, was also negative. It seems reasonable to assume that persisting headache and/or migraine at old age does not increase the risk of cognitive decline.

Cross sectional controlled studies in migraine(104, 105) have suggested the existence of migraine associated cognitive impairment yet the majority of these studies used small samples of clinic-based patients, biased for young age and higher severity of disease and did not control for comorbidities and treatment effects(105).

Nevertheless, findings of an increased incidence of white matter abnormalities and brain lesions associated with migraine has raised the clinical suspicion that migraine patients could have a greater risk of cognitive decline(216, 384). Longitudinal imaging

data failed to show that an association of migraine with progression of such brain lesions; the deep white matter hyperintensities observed more frequently in migraneurs were also not associated with poorer cognitive performance at long-term(385).

Likewise, chronic bodily pain patients have worse cognitive functioning than matched controls in some cross-sectional studies (89, 284) but not in others(387), suggesting the influence of study limitations such as sample sizes, selection bias or psychiatric comorbidity. Evidence of longitudinal changes in long term population studies of other chronic or recurrent pain conditions is lacking, therefore the discussion about the ability of chronic or recurrent to induce neurochemical and/or neoplastic brain changes that potentially could negatively influence cognitive processing is speculative(89). Pain, in general, has not been recognized as a risk factor for dementia(85-87).

Chronic pain and highly recurrent episodic pain of any origin seem to have the ability to influence cognitive performance and to induce a decrease in cortical grey matter volume in areas the central nociceptive system, in particular in areas with relevance for cognitive processing, such as the cingulate cortex, the orbitofrontal cortex and the insula(263). These morphometric changes have no clear correlation to any neurochemical nor anatomical functional abnormalities and may reflect only neuroplastic brain re-organization in response to chronic pain; reversibility of some of these changes has been attained with effective pain treatment(329, 330, 388) supporting the dynamic aspect of pain adaptive brain processes and the findings that all these abnormalities do not seem to have long-term influence on cognitive decline.

This interpretation may not be that simple in older adults, as age is a consistent risk factor for cognitive decline and dementia(85). Even normal heathy older individuals present some age-related decline in cognitive functions (with high interpersonal variability) that is not uniform amongst brain functions – frontal lobe systems show earlier signs of change than do temporal lobe systems(81). Age has been proposed to have a moderating role on in the relationship between chronic pain and associated cognitive changes in one study where a decrease in one task of executive performance was associated with higher pain ratings in younger individuals and to lower pain ratings in older otherwise healthy individuals, with similar chronic pain

duration and analgesic use(389). Another contributing factors are the disability and behavioural changes associated with chronic pain that impair physical capabilities, psychological and social well-being, with negative influence on the healthy aging process (390). Curiously, The effect of age was studied in three longitudinal studies of migraine and only in one an *decreased* risk of decline was found in older (> 50 years) migraine with aura patients(185), while the others failed to find any differences(217, 281). Age has also an impact on the prevalence of migraine, that decreases after the age of 45(391), increasing the complexity of the association between cognitive decline, aging and persisting migraine.

Migraine aura did not seem to influence cognitive decline in our sample nor in other longitudinal studies (185, 217); cross-sectional studies present conflicting findings, some finding evidence of a different cognitive profile between patients with and without aura(211, 282), while other fail to do so(104). Again, methodological differences are proposed to underlie these findings. In our sample, migraine patients progressing to cognitive decline were younger and more likely to have a higher impact disease than those who remained cognitively normal despite no influence was documented regarding attack frequency; the impact of the disease measured in attack frequency has been often associated with impairment in processing speed, attention and memory in some large clinic-based studies but not in larger populational studies(104). Nevertheless, in our sample the total number of migraine patients with cognitive decline was small (4 in total) and these patients had lower literacy, a fact that has clear influence on cognitive performance(77) and therefore limits speculation about the effect of migraine impact found.

An interesting observation in this study is that the in older migraine patients migraine characteristics change over a 5 years timespan; in our sample 31% of the revaluated migraine patients had no attacks in the previous year and those with persistent attacks, the overwhelming majority (65%) has less than one monthly attack. In 55% of patients their attacks ceased to accompanied by nausea, in 30% the photophobia was no longer present and 35% had milder attack impact, being now able to work and function during attacks. These changes in migraine characteristics with aging are documented (17, 377) but clearly influence our ability to diagnose migraine

and to distinguish it from non-migraine headache, being a recognized limitation of our study.

Another study limitations include the high attrition (around 42%) when compared to similar length studies that had retention rates of 80% at 3 years(217), 98% at 5(281) and 75% at 6 years(270) follow up. Possible explanations may include lack of financial compensation for participation and lower population education levels. Migraine patients in or sample were younger, more often females and had higher depression rates and subjective memory complaints, nevertheless their cognitive performance was uninfluenced by these factors(268). The lack of imaging data in our study also limits interpretation of cognitive decline etiology; however vascular risk factors were similar between groups, which argues against the odds of a higher risk for subclinical ischaemic lesions in either group.

In conclusion, persisting migraine and non-headache pain at older age may influence some aspects of cognitive executive performance but is not associated with an increase probability of cognitive decline, supporting that these changes are related to pain adaptation mechanisms and not to pain-associated degenerative processes. These findings suggest that pain control may influence improvement of cognitive functioning at old age, but not the likelihood of having dementia.

6. Summary of Findings, Discussion and Future Perspectives

SUMMARY OF FINDINGS

Research question #1 - *Are cognitive symptoms included in clinical series of migraine patients describing the migraine attack phenomenology?*

A systematic literature review retrieved 28 studies (including 8392 patients) in which cognitive symptoms were described to occur during the migraine attack. This observation supports that cognitive symptomatology is a part of the subjective experience of a migraine attack and is consistent with early historical descriptions of migraine and with everyday clinical experience. The type and pattern of cognitive symptoms differed in each phase of the attack, being more consistently described in the prodromal and posdromal phases than during the headache and affecting executive functions predominantly. Cognitive symptomatology of the aura included complex neuropsychological phenomena probably associated with focal cortical depression.

Research question #2 - *What attack-related cognitive symptoms do migraine patients report? Is there a pattern?*

The overwhelming majority of episodic migraine patients (87.3%) reports having on average 2.5 different cognitive symptoms during the headache phase of migraine attacks, when asked. The frequency of these symptoms occurrence is identical to that the occurrence of migraine defining symptoms (nausea, photophobia, phonophobia and worsening with physical effort) in clinical series of migraine. None of the clinical or demographic variables influences the reporting of cognitive symptomatology.

Some specific symptoms were described very consistently using similar phraseology - lower ability to concentrate (14.7% of symptoms, reported by 37% of patients); difficulty in reasoning (9.8% of symptoms, 25% patients) and being "less able" to think (9.1% of symptoms, 23% patients). Two-thirds of spontaneous described symptoms during attacks can be attributed to executive dysfunction and include attention deficits and decreased cognitive processing efficiency and processing speed.

Research question #3 - *Are attack-related cognitive symptoms relevant to migraine-attack related disability?*

Patients subjectively rate pain as the most relevant symptoms of the migraine attack, both in terms of intensity and disability. Intensity and disability attributed to attack-related cognitive symptoms are rated secondly, being higher than photophobia, nausea and all other migraine defining symptoms. The intensity and disability of attack-related cognitive symptoms correlates to intensity and disability attributed to the attack itself, supporting the relevance of these symptoms in migraine impact.

Research question #4 - *Can we identify and quantify attack-related cognitive symptoms in migraine?*

A fast, inexpensive and universal way to systematically identify and quantify symptomatology is through the use of a questionnaire. A multiple choice 9-item self-administered questionnaire– the Mig-SCog – was developed for that purpose and validated, showing good construct validity, internal consistency, temporal stability and external validity. The questionnaire covers the domains of executive functions (attention, processing speed, orientation, planning) and language (naming, verbal comprehension and sentence production).

Research question #5 - *Are cognitive complaints identified with the Mig-SCog specific for migraine? How reliable is the Mig-SCog?*

Mig-SCog scores are consistently higher in migraine than in tension-type headache, particularly in items related to cognitive functions. Obtaining a high score on the Mig-SCog has a high specificity for the diagnosis of migraine. In migraine patients, the scoring of the Mig-SCog in consistently higher when it relates to migraine than to non-headache pain or being headache free, reflecting again its specificity for the migraine diagnosis. Mig-SCog also showed negligible recall bias when comparing scores obtained by memory of usual attacks to within attacks.

Research question #6 - *What is the evidence of cognitive dysfunction occurrence during migraine attacks?*

A systematic review of medical databases retrieved 10 articles (including 351 patients) with relevance to the study question. Five of these articles had enough data to be analyzed and all were positive in documenting reversible cognitive dysfunction measures by neuropsychological

testing during migraine attacks. The pattern of cognitive dysfunction most often evoked in attacks was dysexecutive however most of the studies were biased towards including more executive function tests. This review disclosed the existence of important study limitations not accounted for in most of the data available, such as controlling for the practice of learning effect bias, for treatment effects, concurrent mood disorders and the occurrence of aura during studied attacks.

Research question #7 - *Do migraine patients have reversible cognitive impairment during attacks?*

Extensive neuropsychological testing within a spontaneously occurring migraine without aura attack revealed a decline in most of the tests performed, although the high attrition prevented most of these changes to attain statistical significance. A significant decrease was observed only in tests of reading and processing speed, verbal memory and learning.

Research question #8 - *How can we measure attack-related cognitive impairment?*

It was possible to obtain a short battery of executive and language tests and to apply it in interictal migraine patients and controls in repeated short-term (6 weeks) applications. The battery was fast and easy to apply with minimal resources. Patients' interictal performance on this battery was identical to that of matched controls and a clinically meaningful predictable score change of repeated applications was identified for each test, therefore fulfilling the basic requirements to test this battery usefulness in determining attack-related cognitive dysfunction.

Research question #9 - *Do brain perfusion changes exist during migraine without aura attacks?*

The existing information about brain perfusion changes during migraine without aura attacks was scarce, inconsistent and used different techniques, some of them updated. Cerebral global and regional brain perfusion evaluated with ASL- MRI was not able to identify perfusion differences in a naturally occurring migraine without aura attack compared to the headache-free status.

Research question #10 - *Are there neuronal network abnormalities underlying the attack-related executive symptoms in migraine?*

The involvement of certain brain areas (such the anterior cingulate and the frontopolar cortex) both during migraine attack and in executive tasks lead to the assumption that evoking cognitive activity in this areas during attack would result either in internal interference or an increase in workload of these areas, that could potentially changes the expected activation pattern or areas in response to the task. Testing this hypothesis with a BOLD-fMRI study using the N-Back working memory paradigm yielded negative results, both in activation patterns but also in concurrent neuropsychological performance evaluation.

Research question #11 - *Is ongoing migraine related to worse cognitive performance late in life?*

Comparing neuropsychological performance of a population-based sample of older adults (aged 50 or over) with persisting migraine, non-migraine headache and headache-free individuals revealed a worse performance of migraine and non-migraine headache individuals in some measures of executive functioning, while most of the tests were comparable to headache-free controls. In particular, migraine subjects performed worse in a test of attention and processing speed while non-migraine headache subjects had lower sematic memory performance and faulty retrieval strategies.

Research question #12 - *Is migraine associated with an increased risk of cognitive decline later in life, compared to other headaches or being headache-free?*

The repeated neuropsychological evaluation of a population based study of older adults (aged 50 or over) in a five years period was ensued to identify cognitive decline in memory and/or executive functions. Having migraine or non-migraine headache did not increase the frequency of cognitive decline (in neither of the domains) when compared to headache-free controls. In patients with migraine who did decline none of the migraine characteristics was associated with an increased risk of decline.

DISCUSSION

Migraine attacks are complex and variable phenomena (inter-individual and intra-individual variability) that are disabling, recurrent and with clinical expression on 3 symptomatic axis - (1) Head pain; (2) Gastrointestinal symptoms; (3) Intolerance to sensorial stimulation(7). Based on shared clinical experience and daily exposure to patients descriptions of "not being able to function", "feeling distracted" or "unable to think" during attacks it was our clinical impression that, based on the frequency and severity of these symptoms, they should be considered as the fourth symptomatic axis of the attacks, and probably as one relevant contributor to attack-related disability(392).

There is, in our opinion, a clinical need to improve knowledge on this topic, to value such symptoms and to improve their control with acute attack treatments; adjusting treatment strategies will improve disease control and decrease migraine-related disability. Additionally, the study of these symptoms represent a window of opportunity to learn about the neuronal mechanisms that are subjacent to them will improve current knowledge on migraine pathophysiology.

Motivation for this studies was patient-driven; our research plan was designed to try to understand the frequency, quality and clinical relevance of these symptoms, and to some extent to explore the neuronal subtract of some attack related changes and the possible long term effects that persisting migraine could have on cognitive performance at later ages.

We screened the literature for studies including cognitive symptoms in the clinical description of migraine attacks, which we have found to be relatively scarce (considering that the first written description we found dated from the first century, by one of Hippocrates disciples, Aretaeus of Cappadocia(8)), yet consistent. From the existing data, the most often described cognitive symptoms included concentration problems, impaired thinking, intellectual disturbances and language difficulties (speech, reading and writing) and were present in all phases of migraine attacks, although less frequently

during the aura phase. We conducted a prospective study screening for the occurrence of cognitive symptoms during attacks that disclosed a very high frequency (87%) of such symptoms and many had very consistent inter-individual descriptions, despite their natural subjectivity. Very frequent complaints included a lower ability to concentrate, difficulty in reasoning and being less able to think, which corroborated nicely data previously obtained from the literature. More importantly, these symptoms descriptions were consistent with the dysexecutive pattern of reversible cognitive dysfunction supported by a literature review on studies including neuropsychological testing during migraine attacks(108). This seemed to support that tasks requiring attention(265) were preferentially involved in the migraine associated brain process, and led to the suspicion that migraine related cognitive dysfunction could be associated with neuronal recruitment of areas involved both in pain processing and attention, such as the anterior cingulated and the dorso-lateral prefrontal (DLPF) cortices (264).

This dysexecutive pattern was not reproduced in our study of neuropsychological performance during attacks, that despite having had a high attrition rate that resulted in a small final sample and therefore less optimal statistical power, it was able to control for the most common bias of previous existing data(108, 109). Nevertheless, our data supported a nominal performance decline in the majority of neuropsychological tests during attacks, when compared to headache-free periods, but most expressively in complex episodic memory tasks, suggesting either temporal(152) or sub-cortical nuclei involvement during the migraine attack (153), both structures found to be activated in functional studies of migraine attacks (152, 153) .

Further supporting the absence of cingulated and prefrontal cortex dysfunction during migraine attacks came from our fMRI- BOLD study, in which the execution of a working memory task during a migraine without aura attack had no influence on the cerebral activity pattern, when compared to the headache-free status. Arguing against significant cortical dysfunction, as demonstrated during auras, we were also unable to identify brain perfusion abnormalities during migraine without aura attacks using the MRI-ASL technique.

Regardless of what the neuronal subtract of attack-related cognitive symptoms in migraine might be, their occurrence is very consistent and relevant to patients and they were found to correlate to attack-related disability(392). As the description of cognitive difficulties can be subjective, it is important in clinical practice and the research settings that they can be identified and graded in a consistent and standardized manner. We developed an adequate tool to identify and quantify specifically migraine attack related subjective cognitive symptoms, the Mig-SCog(118), that we hope will contribute to due valorization of these symptoms.

In our studies we assumed that cognitive performance differed between brain states (attack and pain-free) in migraine patients, in line with patients' complaints, so the pain-free status was used as a control situation to try to identify attack-related dysfunction. Some cross-sectional studies on clinical-based samples of migraine patients suggested that their interictal cognitive performance could be inferior to controls in some neuropsychological tests, suggesting a small effect of migraine in processing speed, attention, working memory, sustained attention, inhibition, verbal memory and verbal skills(105).

We assembled a short neuropsychological battery including executive and language tests and applied it in a small sample of young and healthy episodic migraine patients having a low-impact disease (no prophylactic treatments, low comorbidities) in their interictal (pain-free) status and to matched controls and we were unable to reproduce these findings. Our data is in line with data from population or community-based studies, both cross-sectional and longitudinal, that have been consistently negative in trying to identify cognitive differences of performance or cognitive decline rates of migraine patients compared to controls; in general, these studies have larger samples but shorter and less sensitive neuropsychological evaluations(104, 105).

We additionally studied a large sample of older adults in primary care setting, comparing those with migraine and non-migraine headaches after the age of 50, to non-headache. An extended neuropsychological battery was used in this study that was able to pick up

some minor differences between groups – migraineurs were slightly worse in an attention task while non-migraine headache individuals had more intrusions and worse discriminability in a memory recognition task and lower performance on a semantic memory test. Although there were no differences in the vast majority of tests, these findings suggest the existence of mild dysexecutive dysfunction associated with persisting headache at older ages, either migraine or non-migraine headache(268). We then conducted a 5-years follow-up study of the same sample to screen for cognitive decline and we were unable to document any influence of migraine or non-migraine headache in the risk of decline or dementia, again supporting data from population-based longitudinal studies(104).

FUTURE PERSPECTIVES

Cognitive and behavioral symptoms are a part of the migraine attack that often precede and exceed the painful more disturbing phase. Headache doctors listen to patients' descriptions everyday yet no true appreciation of the importance and impact of such symptoms exists, neither in clinicians nor in researchers. As a small example, the ability to predict attacks and to start treatment early can be of exceeding help in acute pain control and increase cost-effectiveness of treatment (167, 168). Lack of physician awareness prevents adequate treatment strategies, either pharmacological or coaching or life-style adaptations. It also concurs to lack of empathy, and therefor to an increased burden of disease.

Although some work has been done to increase awareness about these symptoms and an instrument was developed that allows their identification and quantification, there is still the need of testing the usefulness of this instrument in measuring outcomes of therapeutic trials or in helping to quantify migraine impact and/or attack-related disability. The potential use of this outcome measure could help to improve acute attack control strategies or to the development of drugs targeting cognitive dysfunction specifically.

Another useful tool would be the identification or development of a brief and practical neuropsychological test to allow repeated short term applications in order to be possible to test migraine patients' executive performance in any given moment. Although a brief neuropsychological battery was assembled and tested to that purpose, it failed to disclose relevant impairment during attacks. Further work should focus on developing

and testing a task designed to disclose the most consistently identified attack-related impairment, in attention and processing speed.

The brain processes underlying attack-related cognitive symptoms in migraine are still elusive, although potentially relevant for understanding migraine without aura pathophysiology and new potential treatment targets that would promptly restore cognitive function aside with pain control. Comparing migraine data to other episodic recurrent or chronic pain conditions will help to clarify some of the mechanisms that could be involved in these processes.

It is possible that our view of the attack related phenomena will change, in line with our current understanding of migraine pathophysiology(28). Migraine could then be understood as a brain *state*, in a given susceptible individual, that sequentially oscillates between syndromic manifestations with a variable frequency or rhythmicity. Extremely relevant issues are the study of the brain processes triggering attack onset and resolution; such knowledge could potentially help inducing a long lasting migraine free state.

The absence of brain perfusion abnormalities in migraine without aura episodes seems to be consistent in most of the published series and was documented with different techniques, so further studies of brain perfusion in migraine patients do not seem advantageous, at least with the technology currently available. On the other hand, studies of brain function in clinical samples seem promising in further elucidating brain changes underlying cognitive dysfunction during attacks with particular relevance to the study of patterns of functional connectivity and of evoked subcortical neuronal function during

attacks. Clinical research of cognitive function during attacks can expand into other techniques that were not explored in the current research project, such as other brain functional studies, neurophysiological studies or the combination of both.

Al evidence supports that migraine related cognitive impairment occurs mostly during attacks. However, repeated persistent or chronic pain is associated with brain changes that seem reversible with effective pain treatment, therefore not contributing to late-life cognitive impairment. As migraine prevalence declines after the forth to fifth decades of life, having migraine does not seem likely to be a significant contribute to cognitive impairment. Nevertheless, data analysis of this problem is complex, as both migraine prevalence, migraine frequency and its clinical expression (in which we base our diagnosis in) change with aging and, on the contrary, age is the most relevant factor associated with cognitive dysfunction and decline. Further studies on this topic should take into consideration all this factors and still be able to evaluate neuropsychological function thoroughly and use large community-based samples. Other important line of future research includes the study of the effect of chronic headache and pain control in the risk of cognitive impairment or dementia.

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Appendix